STUDIES ON GANGLION CELLS.

FROM THE PATHOLOGICAL LABORATORY OF THE ALUMNI OF THE COLLEGE OF PHYSICIANS AND SURGEONS, COLUMBIA UNIVERSITY, NEW YORK.

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STUDIES ON GANGLION CELLS.*

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INTRODUCTION.

Up to a period dating about ten years ago, the knowledge of the pathology of the ganglion cell rested upon the study of tissues hardened usually in chromic acid, and stained by carmine or by Weigert's or Golgi's methods. A rather voluminous literature had accumulated referring to changes demonstrable by these methods, and many of the grosser alterations of the ganglion cells had been accurately described and their significance partially determined. In most of the acute and chronic diseases of the nervous system the condition of the nerve cells had been studied, often exhaustively, and in many diseases affecting other organs, especially the infectious diseases, the lesions in the cells of the central nervous system had been described

*A preliminary communication on these studies was read before the New York Pathological Society, February 9th, 1898.

at some length. Thus we find in such descriptions the terms, granular and cloudy swelling; pigment degeneration; vacuolation; colloid degeneration; shrinkage; loss of nucleus, nucleolus, and processes; increased or diminished staining capacity; rupture of cell body and processes; dilatation of pericellular lymph spaces, and infiltration of this space and of the cell body with small round cells. Based upon the observation of these grosser changes the knowledge of the pathology of the ganglion cell had been very widely extended, and successfully applied in the interpretation of morbid clinical phenomena.

Yet in spite of the prodigious labor steadily devoted to the subject, it cannot be claimed that any systematic basis for the classification of pathological changes in ganglion cells had been elaborated. In fact it had never been determined whether many of the changes described were the result of vital or of cadaveric processes, while it was constantly acknowledged that the described alterations were probably preceded by less marked changes not then demonstrable.

Further, it had long been apparent that existing technical methods failed to reveal a whole series of more delicate cytological changes which must be supposed to result from the action of powerful nerve poisons, in acute intoxications and in diseases proving rapidly fatal with pronounced nervous symptoms. The histological structure of the ganglion cell was practically inaccessible to the investigator, equipped with the ordinary methods for microscopical examination of tissues.

The past decade, however, has witnessed the development of a method of cytological research which has greatly enlarged our conceptions of the structure of nerve cells, and is claimed to demonstrate those finer alterations of

structure which have been obliterated by other technical procedures.

To determine to some extent how far these claims are justified, to ascertain in what these finer cellular alterations consist, and what significance may be attached to their presence, have been the objects of the present study which has occupied the writer during the past two and one-half years. Incidentally, the results bear on the relation of the nervous system to general diseases. The work has consisted in the examination of the nervous system in various diseases, by means of Nissl's and related methods, and in some experimental studies. The full report of these studies necessitates a review of the present status of our knowledge of this method of cytological research and of the cellular changes which it demonstrates.

Section I.

TECHNICS.

In 1885 Nissl[1] called attention to the fact that chromium salts destroy the finer structure of nerve cells, while preserving the fibres, and that if we are to demonstrate the minute structure of the cell, other hardening agents must be used. For this purpose he recommended alcohol as a fixative fluid and magenta red, dahlia, and vesuvin as staining agents. The sections of the tissues thus hardened were to be heated moderately in any of the above dyes, decolorized in alcohol and anilin oil, cleared in benzine, and mounted in balsam. By careful comparison of normal and pathological brains, Nissl claimed to demonstrate pathological changes in the cortical nerve cells which had hitherto escaped detection.

In 1890[2] Nissl recommended the use of methylene blue in watery solution instead of the dyes formerly employed.

Methylene blue had already been extensively used in blood technics by Ehrlich, and had been applied by him in 1886 in the form of intravenous injections to demonstrate some of the finer details of the structure of nerve cells and especially of nerve end-organs.[4]

From what we now know of the great variety of appearances presented by the anterior horn cells of the spinal cord in disease, it is not a matter of surprise that the early experience with this method led to much confusion. All grades of intensity of stain and apparent change in structure were met with under apparently identical conditions, and seemed to be referable to imperfections in the new method. Chromatophilic cells were found side by side with chromatophobic cells, and in some regions all the cells might appear chromatophilic, or, again, chromatophobic. It was hoped to avoid some of these irregularities by improvements in fixation and staining and in 1894[3] Nissl published a very complex procedure for the staining by methylene blue. The tissues, not longer than twenty hours *post-mortem*, were to be hardened in 96 per cent alcohol, and sectioned without being embedded in celloidin. To the methylene blue solution (3.75 parts per 1000 of distil. water) was added, at the suggestion of Frank, of Wiesbaden, 1.75 parts of Venetian soap, and in this solution the section was heated until bubbles were produced. They were then decolorized in anilin alcohol, (anilin oil 10, alcohol (96 per cent) 90), until the dye ceased to be extracted. They were then placed upon a glass slide, dried by blotting paper, treated with a few drops of oil cajeput, dried again, finally treated with a few drops of benzine, mounted in benzine colophonium and heated till all benzine was driven off. The benzine colophonium was made by dissolving colophonium in a

sufficient amount of benzine and allowing the fluid to settle for 24 hours, when the supernatant portion became translucent.

The rationale of this method has not, so far as the writer is aware, been set forth in any of Nissl's publications. All of these modifications of the original method, especially the addition of an alkali in the form of soap, tend to give clearer differentiation of the chromatic bodies, while the above mounting medium was probably devised to prevent the fading commonly observed soon after mounting sections in balsam.

In the hands of various investigators the original and perfected method of Nissl has been submitted to several modifications.

Rehm[5] recommends immediate fixation in strong alcohol as the most generally applicable method for nervous tissues allowing by different staining methods the demonstration of cellular and nuclear structure as well as of fibres. Decolorization in anilin alcohol he finds necessary only in old specimens in which it clears up the deeply blue stained globules of free myelin. In other cases he prefers strong alcohol which in his hands seem to give better differentiation between nerve and connective tissue cells, the former remaining dark blue, the latter assuming a greenish tinge after staining in methylene blue. For the complete differentiation of nerve and neuroglia cells he urges the use of a counterstain, viz.: 1 per cent alc. sol. of fuchsin, in which specimens remain fifteen minutes. The use of some similar acid counterstain has also the advantage of demonstrating the achromatic substance of the cell body.

Lenhossek[6] has secured satisfactory results by hardening specimens in 20 per cent formalin, followed by strong

alcohol. He prefers oil of cajeput as a clearing medium. Staining for five minutes without heat in a concentrated solution of thionin he has found to give very excellent results. Sections thus stained are to be washed in water, decolorized in anilin alcohol, cleared in oil of cajeput, passed rapidly through xylol, and mounted in damarlack or in balsam. He has also secured good demonstrations of chromatic bodies by the use of saffranin, fuchsin, dahlia, and ordinary Bohmer's hematoxylin.

During the past three or four years much of the reported study of Nissl's stain has been made on tissues hardened by corrosive sublimate. This chemical has been used as a saturated sol. in water or in .6 per cent salt sol., or in the form of Lang's fluid: mercuric chlor., 5 grms.; sodium chlor., 6 grms; acetic acid, 5 grms.; aq., 100 grms. All of these solutions have been reported as furnishing very excellent results in cytological detail, and they have been claimed in some instances to have proven superior to alcohol. Flemming[7] who actively supports the fibrillar theory of the structure of ganglion cells, hardens the tissues in sublimate and stains with Delafield's or Heidenhain's iron hematoxylin. Colucci[8] obtains very handsome specimens by hardening in ½ per cent picric acid in water or in alcohol, or in picric acid and sublimate.

Held[9] secures very instructive pictures of the ganglion cells by staining with erythosin and methylene blue. The method is as follows: The specimens are fixed by preference in Van Gehuchten's solution. Alcohol abs., 60; chloroform, 30; ac. glac., 10; or in the following sol.: Sublimate, 1; acetone, 40; aq., 100. The sections are first stained in erythosin, 1; aq. dist., 150; ac., 2 gtt.; which is gently warmed one to two minutes. They are then washed in water and stained in a special sol. of

methylene blue, composed of Nissl's fluid (usual formula) and 5 per cent watery sol. of acetone, each equal parts. In this dye they are warmed till the odor of acetone disappears, then decolorized in $\frac{1}{10}$ per cent sol. of alum till the sections are red; washed in water, dehydrated in alcohol, and cleared in oil of cajeput. By this method the body of the cell appears red, the chromatic masses blue; nuclear membrane red, nucleolus blue, secondary nucleoli violet.

Savdovsky[10] expresses preference for a modification of Nissl's method devised by himself. The specimens are hardened three days in 10 per cent formalin, followed by alcohol. The sections are stained 15 to 60 seconds in 1 per cent sol. methylene blue, or better in a sat. sol. of fuschin in 5 per cent carbolic acid. They are decolorized in 1 per cent acetic acid till the gray and white matter appear differentiated, and finally dehydrated in absolute alcohol.

Smirnoff[11] hardens the tissues in alcohol as usual, but stains 10 minutes to 24 hours in a solution of toluidine blue, 1 part, NaCl .75, water 98, decolorizing in sat. alcoholic solution of eosin, thereby staining the achromatic part of the cell body.

Marina[12] recommends the following mixture as a fixative for nervous tissues. Alcohol 96 per cent, 100 cc.; formol, 5 cc.; chromic acid, 10 cgm. The tissues should remain in this fluid, frequently renewed, for about one week, after which either Nissl's or Weigert's staining methods may be successfully applied.

Graf[13] recommends as a specially valuable fixative for cytological study, mixtures in equal parts of sat. sol. of picric acid in water, and of formalin 5, 10, or 15 per cent. In these fluids specimens should remain from one-half to two hours and then be washed and thoroughly hardened

in alcohols 30–98 per cent. As stains he prefers Heidenhain's iron hematoxylin and Bordeaux red. For the demonstration of fibrillar structure Graf recommends the following mixture: 4 vols. oxalic acid (8 per cent); 3 vols. alcohol (95 per cent); 3 vols. chromic acid, (1 per cent). In this fluid thin pieces of tissue should remain one-half to two hours, after which they are washed in water and alcohol. The sections are to be stained in iron-hematoxylin.

Cox[14] recommends the following mixtures for the demonstration of the fibrils as well as of the chromatic bodies of ganglion cells:

(1)	Sublimate, sat. watery sol.	30	
	Osmic acid, 1 per cent	10	
	Acetic acid (glac.)	5	or
(2)	Sublimate, sat. watery sol.	15	
	Platinic chloride, 5 per cent	15	
	Osmic acid	10	
	Acetic-glac.	5	or
(3)	Sublimate, (sat. watery sol.)	30	
	Formalin,	10	
	Acetic acid, glac.	5	

Specimens should remain in these fluids two to three days and be washed in 60 per cent alcohol. Sections may be stained in Delafield's hematoxylin, by Heidenhain's iron hematoxylin, or by a process specially devised by this author, of which details may be found in the original article.

As a decolorizing fluid, Gothard[15] recommends on various grounds the following mixture, which dissolves celloidin, decolorizes the achromatic substance perfectly,

and sharply differentiates the chromatic structure: Creosote, 50 cc.; oil of cajeput, 40; xylol, 50; absolute alcohol, 160.

Rossalimo and Murawjeff,[16] recommend fixation in formalin both for Nissl's stain and for the demonstration of degenerative products of myelin. They prefer a 2–3 per cent solution for the first two days, replacing this with a 4 per cent sol. in which the tissues may remain indefinitely, to be transferred at leisure to alcohol for complete hardening and embedding.

In addition to many of the fixing agents thus far enumerated the writer has had satisfactory results from the use of a 5 per cent solution of formalin saturated with bichloride. The addition of formalin greatly accelerates the penetration of bichloride, this mixture being quite as active in this respect as Lang's fluid.

After the use of mixtures containing formalin, the cells will be found to stain darker than usual, and to require rather longer decolorization in alcohol. In specimens fixed by this agent, the chromatic network of the small cortical cells appears more distinct than after fixation by most other methods, and the usual tendency to fade has been entirely lacking in specimens now a year old. These effects may all be referable to the distinct action of formalin as a mordant for basic dyes.

Formalin alone in 10 per cent sol. has given very excellent results in the writer's experience. This fluid penetrates with considerable rapidity, and shrinkage of the cell from subsequent hardening in alcohol has been almost entirely lacking. Thin sections are necessary when examining tissues hardened by this agent.

In most of the later cases in the present series, Van Gehuchten's fluid was the hardening agent employed;

(absolute alcohol, 60; glac. acetic, 10; chloroform, 30); and the results were usually satisfactory. There are, however, objections to the use of such an acid as glacial acetic in the study of nerve cells, as this chemical penetrates in advance of the other ingredients of the mixture, and when used alone transforms nervous tissue into a swollen, gelatinous mass.

A very short experience in the use of Nissl's stain furnishes convincing evidence that this field of pathological research is largely a study of microscopical technics. The almost infinite variety of appearances presented by nerve cells treated by this method and its modifications, has left the subject, even after the labors of a decade, in a state of considerable confusion. We meet on the one hand with the denial by Trezebinski,[17] Kronthal,[18] Fisher,[19] Held,[9] and others that the chromatic masses, the principal element demonstrated by Nissl's method, exist as such in the living cell, these investigators claiming that they are the artificial products of fixative agents and cannot be seen in fresh specimens or in frozen sections. Held furnishes apparently undeniable proof that the minute structure of the chromatic bodies may be altered at will by varying the strength of the alcohol in which the tissues are fixed, and the same writer finds that chromic acid in 2 per cent solution precipitates the chromatic substance in finely granular condition, and in 1 per cent solution causes it to appear nearly homogeneous, while a solution of ammonium bichromate leaves it entirely homogeneous.

These and similar observations indicate merely that the chromatic substance exists in the cell in fluid form, and while we are dealing in the hardened section with an arti-

fact, it seems probable that it is an artifact that under uniform conditions will give a uniform appearance. It does not seem, therefore, to be a matter of prime importance in the choice of a fixative agent, whether it fixes the chromatic substance in fine or coarse granules or in a homogeneous mass.

A much more difficult question in technics is encountered in the diffuse dark blue stain presented by many cells after treatment with methylene blue and denominated by Nissl "*the chromatophilic condition.*" It has been claimed by Flesch and Koneff[20] that this quality is a normal character of the cell, indicating a distinct physiological condition. Nissl[21] very early and rightly, as it seems, concluded that this character is artificial, and is devoid of pathological significance, resulting from accidental and as yet undetermined effects of hardening agents or from post mortem change. In the writer's specimens prepared after hardening in Lang's fluid the chromatophilic cells were found in greater numbers than in those tissues hardened in alcohol, especially in the outer zones of the blocks of tissue. On various grounds it seemed probable that the acetic acid in Lang's fluid, which penetrates in advance of the bichloride, might be responsible for this peculiarity—a suspicion which was proved to be at least partially correct by the following experiment. A small segment of the medulla of a fresh case was subjected for 24 hours to the action of a 5 per cent sol. of acetic acid. as found in the composition of Lang's fluid, it was then hardened in alcohol, and sections 15 μ in thickness were stained in the usual way. The cells without exception were found stained darkly and diffusely blue, separate chromatic bodies being distinguishable in a very few instances only. An adjoining segment from the same

medulla hardened in alcohol gave very few chromatophilic cells. The writer, therefore, discarded the use of Lang's fluid as a fixative agent on account of the disturbing action of acetic acid. Incidentally, the result stands at variance with the statement that immersion in weak acids dissolves the chromatic bodies as reported by Eve,[22] whose experiments, however, were conducted on sympathetic ganglion cells.

The chromatophilic condition is however too frequent in occurrence and too irregular in distribution to be always referable to a uniform cause, such as the action of fixatives. Not rarely a markedly chromatophilic cell may be seen immediately adjoining a perfectly normal cell, and such a combination is difficult to understand, on the theory of irregular penetration of fixative agents or from the action of any abnormal chemical agent spontaneously produced in the tissue after death.

In the study of post mortem and putrefactive changes, to be considered later, the writer finds no evidence that the chromatophilic condition may result from such processes. In fact, in fresh nerve tissues smeared, dried and stained on a glass slide, distinctly chromatophilic cells may be found. Turner,[23] has also seen them in fresh specimens examined in Farrant's solution and stained with methylene blue.

From a study of the conditions under which these chromatophilic, perfectly opaque and homogeneous cells are found, the writer has been convinced that two principal factors are responsible for their production: (1) If the entire thickness of an ordinary section (15—20 μ) is occupied by a compact normal cell, which is imperfectly decolorized, that cell may appear homogeneous and very darkly stained. For the majority of cells seen in any

particular section of tissue do not extend throughout the section, and it is usually possible to find in every section, no matter what its thickness, some portions of cells which are excessively thin and clear, while others are very dark. (2) When the chromatic bodies have been uniformly and minutely subdivided, it may be impossible, even in comparatively thin sections, to detect these resulting granules and the cell if fully stained, and especially if somewhat shrunken, may appear very dark and homogeneous. The writer has rarely encountered distinct examples of the chromatophilic state which could not be referred to one or both of the above conditions. (Cf. Heimann, loc. cit. p. 319) Kreyssig,[24] Trezebinski,[17] and Nissl,[21] have noted that as a rule the chromatophilic cells are much shrunken, leaving wide pericellular lymphatic spaces.

The *formation of vacuoles* has long been recognized as one of the necessary imperfections in most methods of fixation of nerve cells. Kreyssig,[24] observed vacuoles in the majority of normal ganglion cells preserved in Mueller's fluid. From observations of Trezebinski[17] and others it appears that vacuolation is more frequent after hardening in chromium salts than with other fixatives, but its occurrence in normal specimens after fixation in alcohol and bichloride has been repeatedly noted. Yet vacuolization in any marked degree is regarded by most authorities as of distinct pathological significance. The complete absence of vacuoles has been noted in ganglion cells examined in the fresh condition by Kreyssig,[24] Trezebinski,[17] and Held,[9] with whose observations the writer's experience accords. Held very graphically describes and depicts their formation in fresh ganglion cells on the addition of water to the crushed

tissues. He finds that fine vacuoles first appear in and about the chromatic bodies, that they swell markedly on the addition of water, and that their size and contour in hardened specimens varies much with the different fixatives.

The writer cannot agree with the statement often seen that vacuolation may be regarded as pathological only when it is found in advanced degree. Among the present cases, extreme vacuolation when found, was always plainly referable to post-mortem processes. The study of cadaveric changes in ganglion cells indicates that vacuoles are one of the most constant of post-mortem products; and that they frequently form in considerable numbers and of large size within a few hours, often preceding other post-mortem changes. Especially when the brain and meninges are œdematous, or when the patient has suffered from general sepsis, vacuolation of cells may be expected unless the tissues are fixed very shortly (one-half hr.) after death. The above observations, as well as the circumstances under which vacuoles are usually found in stained specimens, indicate that in the great majority of instances vacuolation of ganglion cells is a cadaveric or artificial product, and in any case with the present state of our knowledge is devoid of definite pathological significance.

The practical indications for the avoidance of this artifact are, then, the rapid fixation of material as fresh as possible, by means of a rapidly penetrating fluid of high osmotic power. A saturated solution of bichloride in normal salt solution recommends itself for this purpose and in the writer's hands has given results very little disturbed by vacuolation, but its slow penetration requires that thin pieces of tissue only should be used. Formalin is also very reliable in this respect.

Under many conditions, the nucleoli of ganglion cells presents spherical transparent globules often projecting from the edges of the nucleolus and frequently spoken of as *nucleolar vacuoles*. It is doubtful if these appearances are to be regarded as of similar character with the vacuoles of the cytoplasm. It appears more probable that they represent subdivided portions of the acidophile substance normally found at the centre of the nucleolus. This appearance of the nucleolus was observed in some degree in all the cases of the present series, but the irregularity of its occurrence has made it impossible to draw any conclusions as to its real nature and significance.

The shrinkage caused by strong alcohol is one of the chief objections to its use in the Nissl method. Many of the instances of the chromatophilic condition are doubtless referable to this action. The appearance of large pericellular lymph spaces about irregularly shrunken cells and of peculiar folds in the nuclear membrane are nearly constant artifacts resulting from this method of fixation. So constant is this result that Lenhossek,[60] was led to believe in the normal existence of a considerable free space about the spinal ganglion cell, an artifact which he now largely avoids by perfect fixation of fresh specimens in sublimate 1; acetic 40; aq. 100, as previously adopted by Flemming. This fluid may, therefore, be recommended as a fixative in this respect. One of the chief advantages of formalin as a fixative is the usual absence of shrunken cells in tissues hardened in this agent.

Besides the examination of stained sections of hardened tissues, other methods of study deserve notice in this connection. 1st. The staining of living nerve cells by the intravenous injection of methylene blue as introduced by Ehrlich,[4] has demonstrated some of the finer details of

the fibrillar structure of sympathetic nerve cells and of terminal end-organs, and the results of this method have important influence on the views now held as to the significance of the chromatic bodies demonstrated by other methods. 2d. The study of fresh portions of nervous tissue crushed under a cover glass and stained by methylene blue as practiced by Thanhofer,[25] Kronthal,[18] Held,[9] Turner,[23] and others, or spread on a slide, dried by heat, or teased in salt solution, has proven of similar import. Arnold[26] macerates small pieces of the gray matter for 2 to 24 hours in 10 per cent sol. of K. I. to which a few drops of Tr. Iodine are added, and examines the fresh specimens stained by eosin. 3d. The pictures furnished by frozen sections stained without the action of any fixative agent cannot be ignored in discussing the structure of the living nerve cell.

By far the clearest demonstration of the cyto-reticulum, of the relation of the so-called achromatic and chromatic structures of the cell, and of the structure of dendrites, secured by the writer, has been obtained in freshly and finely teased specimens of gray matter, fixed by heat and stained by methylene blue and erythrosin. This method cannot, however, be recommended for general purposes, as the large majority of cells are destroyed and the thicker portions of the cells, especially the perinuclear region, are usually found very dense and obscure.

Summary.

Fixation.—To summarize the observation on technics it may be said that alcohol 95 per cent to 97 per cent is most generally used as a fixative. Its superiority consists in its convenience and the compact appearance of the chromatic structures which it insures. Its great disadvantages are

the shrinkage of cells, which is usually very annoying, and its comparatively slow penetration.

The writer believes that a saturated solution of bichloride of mercury in .6 per cent salt sol. is superior to alcohol for many of the purposes of Nissl's stain, and that a saturated solution of bichloride in 5 per cent formalin (or more) is superior for the demonstration of the chromatic network.

Van Gehuchten's fluid, absolute alcohol, 60; chloroform, 30; ac., 10, is to be recommended for the study of a fibrillar structure of the cell.

The writer is at present using formalin 10 per cent as the initial hardening agent. Its results with Nissl's stain are good, and Weigert's staining method may also be employed after such hardening, but not always with success.

The fluid recommended by Marina,[12] alcohol 96, 100 cc.; formalin, 5 cc.; chromic acid, 10 cgm., deserves trial, as it is said to permit of the use of several staining methods.

More important than the choice of any particular fixative is the care in handling the tissues, and the exclusive dependence upon thin pieces of tissue, 1—2 mm., which can be rapidly penetrated by all agents.

Embedding.—Very thin sections, 1 μ, must be cut in paraffin. Properly hardened tissues may be cut 3—5 μ, in celloidin, which is quite thin enough for most purposes. For permanent preservation, tissues embedded in paraffin are superior.

Staining.—The writer has been unable to find any advantage in the addition of soap or any other alkali to the simple 1 per cent solution of methylene blue in water; nor do any of the related dyes possess distinct advantage

over methylene blue. In decolorizing it is important that the alcohol last used should be entirely free from dissolved methylene blue. There appears to be no distinct advantage in the addition of anilin oil to the decolorizer. Erythrosin is superior to eosin as a counter-stain and should be used after the method devised by Held and previously described. Heidenhain's hematoxylin is to be recommended for the demonstration of the fibrillar structure of the cell.

Oil of cajeput gives clearer demonstration of the chromatic structures than any other clearing agent. Specimens hardened in fluids free from acids, cleared in this oil, and mounted in Canada balsam, do not fade seriously, at least within two years.

Section II.

HISTOLOGY.

The Structure of the Chromatic Substance.

The employment of Nissl's stain at once greatly enlarged the knowledge of the histology of the ganglion cells, and although the chromatic bodies had been previously seen and described by Flemming[27] in 1882 and were remarked simultaneously by Benda[28] and Nissl[1] in 1885, it was entirely owing to the excellence of the technical methods devised by Nissl that this investigator was enabled in a comparatively short time to propose a new classification of nerve cells based upon the character of their chromatic substances.

Nissl[29] divides all nerve cells into two main divisions: 1st. The small ganglion cells, *karyochromes*, of which the distinguishing characters and basic staining elements are

to be found in the nucleus. 2d. The larger cells, *somatochromes*, of which the distinguishing characters and chromatic substances are to be found in the body of the cell.

In the first division he distinguishes: 1st, as *karyochromes*, those cells containing a small amount of chromatic substance about a rather small nucleus, as in the cells of the *substantia gelatinosa of Rolando*, and 2d, as *cytochromes* those cells whose nuclei never exceed in size the nuclei of neuroglia cells, as in the cells of the granular layer of the cerebellum.

In the 2d division, *somatochromes*, are the majority of ganglionic cells, whose distinguishing characters are found in the chromatic substance of the cell body, and of which four main groups may be distinguished.

1st. *Archyochromes* (*archos*, network) in which the chromatic substance is found about the nucleus in the form of a fine network, often producing a longitudinal striation, as in the pyramidal cells of the cerebral cortex.

2d. *Stichochromes* (*stichos*, spindle) in which the chromatic substance is found as a series of lenticular spindles or masses composed of fine granules arranged parallel to cellular and nuclear borders, as in the anterior horn cells of the spinal cord.

3d. *Archystichochromes*, of which the body shows a combination of the structures of the two preceding varieties, as do the cells of Purkinje.

4th. *Gryochromes* (*gru*, granule) in which the chromatic element is in the form of granules irregularly placed throughout the cell body, but usually forming threads or heaps, as in the cells of the *corp. striatum.*

All types of cells may show variations in the quantity and compactness of the chromatic substance. Those in

which the chromatic bodies stain intensely with methylene blue are indicated as *pyknomorphous*; those which stain faintly, *apyknomorphous;* while the intermediate grades are denominated as *parapyknomorphous.*

In the *chromatophilic condition* the cell appears shrunken, intensely stained and almost homogeneous, the outlines of nuclei and chromatic bodies being faintly or not at all visible. This condition Nissl regards in all cases an artifact.

The classification of Nissl was proposed merely as a provisional plan for the description of ganglion cells and in spite of many practical and theoretical objections to it, has been widely adopted as a temporary convenience.

The objection most powerfully urged against such an early attempt at classification is the fact that in only two types of cells has the finer structure been thoroughly investigated by this and complemental methods—namely the anterior horn cells of the spinal cord, and the cells of the posterior spinal ganglia.

Benda[30] urges against this classification the lack of purity in the type of cells, finding many transition forms between the various groups of Nissl and more reasonably the supposition that the chromatic masses are not preformed elements of the cell but depend in form upon other fixed constituents of the cytoplasm.

These and other similar considerations have, however, proved inadequate criticisms against a classification based upon very distinct grosser morphological differences.

The further attempt of Nissl[34] to connect the various morphological characters of the cell with distinct physiological functions has been much less successful. In only one group of cells, the stichochromes of the anterior horn of the spinal cord and medulla, does it seem probable

that a distinct function is indicated by a particular type of cell, and as the question is summarized by Van Gehuchten,[31] the facts at present, while not in opposition to this view, are quite insufficient to be convincing. Van Gehuchten admits that the same type of cell under like conditions always presents the same structure, as in the cells of origin of all peripheral motor nerves, the cells of the spinal ganglia, the olfactory bulb, the *cornu ammonis*, etc.

Colucci,[32] distrusts this particular claim of Nissl on the general ground that the data are too few to warrant a classification based on one peculiarity of the cell, while ignoring its features demonstrable by other methods, such as that of Golgi.

Lenhossek,[33] regards the arrangement of chromatic substance in ganglion cells as a purely empirical fact without known significance, and holds that we cannot begin to classify nerve cells until we know how and why structural features stand in causal relation to functional qualities.

A more concrete objection is urged by Benda,[30] who finds that no nucleus is composed exclusively of one type of cell, while impurity in the type is very generally observed.

To these and other similar criticisms Nissl[34] replies that the undoubted existence of transition forms is no essential objection to his scheme of classification; that he does not claim to have settled the whole question of the relation of structure and function, but insists only that the stichochromes of the anterior horn represent typical motor cells.

The strength of this position it is impossible to deny, but it remains for future investigations to determine how far this morphological criterion may be applied to other varieties of cells.

As already stated, in only two types of cells has the minute structure been thoroughly studied by Nissl's and supplemental methods—in the stichochromes of the anterior horn of the spinal cord and the cells of the spinal ganglia.

Structure of the Anterior Horn Cells of the Spinal Cord.

The anterior horn cells are bipolar or multipolar cells, which vary in diameter from 60 μ to 120 μ. Their most striking feature is the arrangement of the chromatic substance in the form of irregular masses, spindles, or large granules, which are found thickly and concentrically grouped about the nucleus, lying parallel to the cell borders, and drawn out into thin rods in the dendrites. Dogiel[35] alone has been able to trace the chromatic bodies into the axis cylinder process, which is generally regarded as being entirely free from chromatic substance, as first noted by Benda[28] in 1885. At the bifurcation of processes is often to be found a distinct triangular mass of chromatic granules called the *bifurcation cone.* Often a crescentic mass is closely applied about a segment of the nuclear membrane, and is called by Nissl the "nuclear cap," a body that is more uniform and distinct in the bipolar cells of the posterior horn of the spinal gray matter. In the spinal stichochromes and spinal ganglionic cells the point of origin of the axis-cylinder process is marked by a crescentic area devoid of chromatic bodies. This area is absent in the ganglionic cells of the retina (Dogiel[36]), in Purkinje cells, and in the cortical pyramidal cells.

The Chromatic Bodies.—It has been generally accepted that the chromatic bodies are composed of a conglomeration of fine granules, although some writers have claimed

that they were occasionally homogeneous. The researches of Held must be admitted to have definitely proven that, treated with the usual fixatives, alcohol, bichloride, etc., they are usually granular, the size of the granules varying with the fixatives employed. (See discussion on technics, page 265.)

Both Held and Nissl agree that in some instances the thinnest sections fail to show any granular structure in the chromatic bodies. In this connection Nissl[37] refers especially to the finely reticulated but not at all granular structures of these bodies in the motor cells of doves and some other animals.

On the question of the state of the chromatic substance in the living cell, opinions have long been at variance. Kronthal,[18] in 1890, examining freshly crushed specimens of spinal gray matter, dried and stained with methylene blue, failed to find any formed chromatic bodies, although the cells were otherwise well stained. Fisher[19] also concluded that the chromatic bodies resulted from the action of fixing fluids, while the living protoplasm of cell is homogeneous.

The studies of Held[9] have furnished important evidence in regard to the condition of the chromatic substance in the living cell. Examining freshly crushed specimens he was unable to find any trace of chromatic bodies in the anterior horn cells of the rabbit. Continued observation showed the appearance of small vacuoles in the cell body and the gradual accumulation about them of fine granules. Cells in this stage fixed in strong alcohol, showed the vacuoles to be located in the centres of chromatic bodies, while the granules proved to be particles of chromatic substance. He therefore concludes that the bodies of Nissl are a precipitate from a previous fluid substance

which is thrown down by fixing agents. The fact that the chromatic bodies become slowly visible when fresh cells are treated with a weak solution of methylene blue he refers to a coagulating or fixing action of the methylene blue.

In a later article he somewhat alters this view, stating that the chromatic bodies appear in the cell within one-half hour after death, without the use of fixing agents, from a process of coagulation occurring as a part of cadaveric changes. In cells examined within three minutes after death he was still unable to find any traces of formed chromatic elements. He finds that 80 per cent alcohol to which has been added $\frac{1}{40}$ to $\frac{1}{4}$ per cent of NaOH fails to precipitate the chromatic substance, which is soluble in alkalies. After treatment with alkalized alcohol the chromatic bodies may still be precipitated by the action of weak acids (after Van Gehuchten's formula, absolute alcohol, 60; chloroform, 30; ac., 10).

The cadaveric precipitation, occurring generally within 12 hours after death, Held refers to the acidity of the central gray matter, which has been shown by Gescheidlen[38] to increase after death.

The writer has repeated Held's experiments with the fresh anterior horn cells of the rabbit, and is convinced that the chromatic bodies are homogeneous in the natural state, that they make their appearance in finely granular form shortly after death and may be demonstrated by weak solutions of methylene blue, either in the moist condition, or in specimens teased after Kronthal's method, or in frozen sections.

Held's studies seem to have proven that the chromatic substance is originally semi-fluid, but it does not appear that this fact interferes essentially with the present views

as to the significance of this constituent of the cell. On the essential point as to the location of the chromatic substance in the living cell, there is no evidence to show that it differs at all from the position in which it is found in stained sections. Moreover, there is no evidence to show that the chromatic substance, whatever its nature may be, is altered in any important respect during fixation, or that it does not pre-exist in some form as a separate constituent of the cell, or that demonstrable variations in its character are not significant of vital processes in cell body.

Dogiel[39] claims that the mere fact that the living protoplasm of the cell is homogeneous is no proof that the chromatic bodies do not exist as such in the natural state, as their refractive power may be the same as that of the cell protoplasm. In his hands a very weak solution of methylene blue in .6 per cent salt solution stains the chromatic bodies well in 5 to 8 minutes, and yet this fluid cannot be said to kill the cell in that time, or at least is not active enough to precipitate the chromatic substance, for cilia, and spermatozoa, and various living larvæ, stain well but remain active for a long time in weak solutions of methylene blue.

There remains to be mentioned in the structure of the chromatic bodies the presence of a ground-substance in which, according to most authorities, the fine granules appear to be embedded, after staining by erythrosin and methylene blue as recommended by Held. This ground-substance appears of a violet color, and where the chromatic granules have been dissolved by alcohol, the ground-substance remains behind unaltered.

Juliusberger[40] demonstrates this substratum of the chromatic bodies by staining thin sections in iodine green

and fuchsine, after which treatment it appears identical in color with the achromatic portion of the cell body.

Van Gehuchten[41] speaks of the chromatic substance as an incrustation on the achromatic reticulum, and identifies the substratum of the chromatic bodies with the achromatic reticulum.

The writer's study of cells which in pathological conditions have lost their chromatic bodies, especially as seen in freshly teased specimens dried and stained on a glass slide, led to the same opinion that Van Gehuchten holds.

An interesting and important inquiry relates to some chemical properties of the chromatic substance. As above noted, Held succeeded in dissolving this substance by weak solutions of NaOH and by concentrated solutions of lithium carbonate, and showed that it is insoluble in weak and concentrated mineral acids, such as nitric, hydrochloric, and by acetic acid.

Eve,[22] on the contrary, found that when sympathetic nerve ganglia were left in weak acids before hardening, the chromatic bodies disappeared, the cell staining diffusely pale blue. There is no apparent explanation of these entirely opposite results. Repeating the experiments of Held, the writer was unable to destroy the chromatic bodies by treatment with several mineral and organic acids, although a raggedness of outline was observed after prolonged (12 hours) exposure to strong solutions. A sat. sol. of lith. carb. also, contrary to the results of Held, did not destroy or alter the chromatic bodies of the medullary cells, although the tissue swelled to twice its natural size in the course of an hour. A weak solution of ammonia, however, completely destroyed all trace of chromatic substance in portions of tissue immersed in this fluid for one hour.

Held found that by treatment with pepsin in a sol. of HCl, at 40° C., the cell body is entirely dissolved, leaving the chromatic masses intact. Millon's reagent he finds to have no effect upon them. Submitted to Lilienfeld's and Monti's microchemical tests for phosphorus the chromatic bodies reacted slightly, and Held concludes that the chromatic substance belongs to the nucleo-albumens. The microchemical reactions of this substance abundantly show that it is not identical with nuclear chromatin.

Benda[30] regards the chromatic granules as related to the basophilic granules of Ehrlich, a supposition combatted by Nissl, Colucci[8] and Heimann,[64] and readily disproven by treatment of sections by Ehrlich's dyes, toward which they do not behave as strictly basophilic bodies, but show characteristic amphophile tendencies.

The Achromatic Portion of the Cell.—Two opposite views are at present actively supported in regard to the structure of the achromatic portion of the cell. The presence of fine fibrils passing diametrically through the cell, with numerous anastomoses, giving often a fine reticular appearance is maintained by Nissl,[42] Becker,[43] Benda,[44] Flemming,[45] Kronthal,[18] Lugaro,[46] Dehler,[47] Dogiel,[36], [39], and many others.

Becker demonstrates these fibrillar structures by Weigert's copper and hematoxylin stain, Kronthal by staining freshly crushed and dried specimens with methylene blue, Flemming by hardening in chromic acid in the chromosmic acetic acid mixture, or with sublimate, and staining with Heidenhain's or Delafield's hematoxylin. Dogiel stains the fresh sections with $\frac{1}{10}$—$\frac{1}{4}$ per cent sol. of methylene blue, having fixed the specimens at various intervals in picrate of ammonia, and demonstrates structures that appear to escape other methods.

On the other hand Lenhossek,[48] Van Gehuchten,[49] Cajal,[50] and Held,[9] are equally confident that the fibrillar structures described by others are not true fibres but rows of fine granules which give the achromatic substance a reticular and spongy appearance.

The latest studies of Held are most convincing of the correctness of this view and that the appearances seen after the cells have been hardened in various fixatives are indistinguishable from those described by Butschli in fluid albumen treated in the same manner. It seems possible, however, that Held, Lenhossek, and Cajal, are not discussing the fibrillar structures that are demonstrated by Dogiel in the retinal cells.

At any rate it is at present impossible to determine which of the two views of the structure of the achromatic part of the cell is correct. The fibrillar theory is most generally accepted, but cannot be said to be the most thoroughly supported. That the achromatic portion of the cell is nevertheless concerned in the function of conducting impulses appears very probable from various theoretical considerations, among which may be mentioned that the continuation of the axis cylinder process is exclusively with this portion of the cell, and that this process is usually composed entirely of achromatic substance, as determined by Simarro[51] and Schaffer.[52]

In addition to the fibrils or granules composing the achromatic substance, other larger granules of somewhat similar staining reactions have been described by Benda,[30] Becker,[43] Levi,[53] and others. It has been claimed by some that these granules represent the metabolic products of the cell (Becker) and that they are increased in number after fatigue of the cell. But little attention has thus far been paid either to the existence or the significance of these elements.

It falls without the scope of this article to more than mention the nearly constant presence of yellowish granular pigment in the adult ganglion cells. This pigment has been shown by Rosin[54] to be related chemically to fat, usually staining black with osmic acid. The presence of this variety of pigment is probably always pathological. A second variety of granular pigment not at all related to the former is found in the cells of the spinal ganglia, sympathetic ganglia, *loc. ceruleus*, *substantia nigra*, etc. The development and distribution of this form of pigment has been studied at some length by several writers, recently by Pilcz,[55] but the relation of the masses and granules to the other elements of the cell still remains unknown.

Nucleus.—The structure of the nucleus of the ganglion cell is rather incompletely shown by Nissl's method. Methylene blue demonstrates a large vesicular nucleus, with a distinct nuclear membrane, a large central nuceolus and occasionally one or more secondary nucleoli (Held), while its further structure is either entirely invisible or is indicated by a fine network of granules stretching from the nucleolus to the nuclear membrane. Some of the various counterstains used in connection with Nissl's method, as the erythrosin of Held, demonstrate the finer structures of the nucleus and their different microchemical reactions.

The ammoniacal carmine solution recommended by Rehm[5] as a counterstain with Nissl's method (carmine, 1; liq. amm. caust., 1; aq. 100, stain 5 min. then decolorize five minutes in alcohol, 100, KNO_3, 1), demonstrates in the centre of the nucleus a rose red mass, which this author seems to regard as a vacuole. With this distinguishing test, he has never been able to find more than

one nucleolus in the normal cell. The writer finds that the central acidophile portion of the nucleolus is brilliantly demonstrated in sublimate preparations by Ehrlich's tricolor fluid, after decolorization in alcohol, nor has he succeeded in finding any such central body in the numerous granules resembling secondary nucleoli to be found in pathological specimens.

According to Levi,[56] all the true chromatin of the nucleus is concentrated in a series of granules lying along the edge of the nucleolus, while the rest of the nuclear network consists of linin.

The writer's study of the structure of ganglion cells has led to conclusions which in one particular, namely, the relation of the chromatic bodies and reticulum to the achromatic or acidophile reticulum are at variance with the views generally accepted. These conclusions are based upon the examination of ganglion cells in normal and pathological conditions, fixed in various fluids, principally Van Gehuchten's, stained in section by methylene blue and by erythrosin and methylene blue, and of freshly teased specimens fixed by heat and stained by the same fluids. In very thin sections of cells prepared as above, by the use of artificial light (32 candle power electric arc), by applying oil to the condenser as well as to the lens (Zeiss apochromatic $\frac{1}{12}$) very clear demonstrations of the cyto-reticulum are obtained. This reticulum is remarkably clear and the relations of the chromatic and achromatic structures appear especially distinct in freshly teased specimens fixed by heat (100° C., 5 min.) Under the above conditions it appears to the writer that the chromatic structures in the cerebral, spinal, and spinal

ganglionic cells are always found in the form of a reticulum with nodal thickenings, which in the stichochromes, reach a considerable volume, covering often several adjoining meshes of the network. The connecting threads of the chromatic reticulum are very delicate in the spinal stichochromes, Plate I, Fig. 1; and spinal ganglionic cells Plate I, Fig. 4; and rather coarse in Purkinje cells, Plate I, Fig. 2.

The presence of this chromatic network is more plainly shown in cells deficient in chromatic substance, in which the fading chromatic bodies may often be seen to resolve themselves into a uniform and delicate chromatic network. (Plate V, Figs. 1 and 2; Plate VI, Fig. 4).

Moreover, a significant pathological lesion, it is believed, consists in partial or complete disintegration, apart from simple fading of nodal thickenings, of this chromatic reticulum. (Plate VI, Fig. 1).

The chromatic bodies and network, as conclusively shown by Held, may appear granular or homogeneous, according to the methods of fixation employed. These conclusions have reference solely to the morphology of the cell in hardened tissues and may have little or no bearing on the relations of the chromatic substance in the living cell.

The results of the present study indicate also that the achromatic or acidophile reticulum depicted by Held is fully demonstrable in specimens stained by methylene blue alone, and is continuous and identical with the chromatic reticulum which the writer has been discussing. Freshly teased specimens fixed by heat and stained by erythrosin and methylene blue are specially convincing of the correctness of this view. In such specimens of the normal human lumbar stichochromes the main dendrite

and adjoining portion of the cell body, an area which may be conveniently termed the "*polar dendrite*" may sometimes be found drawn out into an extremely thin layer, and under these circumstances the relations of the chromatic and achromatic portion of the cell are remarkably distinct. *Here a single reticulum is demonstrable, stainable alike by methylene blue or erythrosin, and when both dyes are used the thinner strands of the reticulum appear bright red while the nodal thickenings are blue.* Moreover, the blue masses fade insensibly into the red and both are everywhere continuous. The meshes of the reticulum are either clear or contain isolated acidophile granules of the same character as the substance ensheathing the dendrites and cell body and continuous with the axis cylinder process.

These indications of the relation between the so-called chromatic and achromatic reticulum accord with the observations made upon sections of hardened tissue stained by the same dyes.

In regard to the strictly achromatic substance of the cell, specimens of the "polar dendrite" prepared as above, show the presence of a granular acidophile substance ensheathing the dendrites, continued in a layer of varying thickness about most of the cell body, visible in many of the meshes of the reticulum, and composing exclusively the axis cylinder process. This substance appears to be identical with the "*axis cylinder geflechte*" of Held, but the accompanying fibrils as well as the serial arrangement of the granules, beautifully shown in Held's drawings, were not visible in the writer's preparations. This view of the structure of the body of the nerve cell appears to be identical in most particulars with that recently formulated by Van Gehuchten.[41]

The appearance in the writer's specimens, however,

fully accord with the observations of Schiefferdecker,[57] Dogiel,[58] Held,[9] and Apathy,[59] that the dendrites contain a granular substance identical with that found in the axis cylinder process, a fact which strongly indicates that all these processes share the function of conducting impulses.

Spinal Ganglion Cells.

The cells of the human spinal ganglia have been exhaustively studied by Lenhossek,[60] Held,[9] Flemming,[61] Nissl,[62] Cox,[63] and Heimann,[64] from whose descriptions the following outlines have been extracted.

These cells are of large size, 60–80 μ in diameter, at times reaching 120 μ. Each cell is surrounded by a connective tissue capsule, often very cellular, and lined by a layer of flat endothelial cells which Lenhossek regards as furnishing nutriment to the contained ganglion cell. The capsule, in the natural condition, is entirely filled by the nerve cell, but in most stained specimens shrinkage of the cell creates an artificial space within the capsule. The cells are unipolar, the process being attached to the body in a knob-like projection, marked off from the rest of the body, as a clear achromatic crescentic area. The chromatic substance usually appears in the form of rather small granules which are distinctly more numerous about the nucleus, but are wanting in a narrow zone adjacent to the nuclear membrane, in a narrow peripheral zone, and at the crescentic area giving origin to the single process. This type of spinal ganglion cells belongs to Nissl's class of gryochromes.

Other less numerous cells contain larger chromatic masses, resembling in structure the spinal stichochromes, while Flemming has described a third class of cells of

moderate size, staining usually rather dark, and containing very coarse granules of chromatic substance. A considerable variation in staining quality may be noted in the cells of the spinal ganglionic cells, a feature referred by Lenhossek to the greater density of the protoplasm, especially of the smaller cells.

Cox describes two main varieties of spinal ganglionic cells. One type contains large or small irregular chromatic bodies without distinct concentric arrangement. The cells of this type may be either large or small. Another type of cell contains large irregular chromatic masses in definite concentric arrangement.

Heimann, in a recent study of the cells of the spinal ganglia in rabbits, especially of their reaction to various dyes, seems to identify the cyto-reticulum with a fibrillar structure. He finds that the chromatic bodies are not continuous with these "fibrils," and he speaks of but one type of cell.

From the study of the cells of the spinal ganglion in the present cases, the writer was unable to find convincing evidence that these ganglia contain more than one distinct variety of cell. (See Plate I, Fig. 4.) While the peculiarities of the chromatic bodies above detailed were noted in many instances, there were indications that these features depended upon physiological or pathological variations rather than upon distinct differences in normal histological structure.

Various grades of pigment deposit, increasing with age, may be found, especially in the larger cells.

The structure of the achromatic portion of the cell may be regarded as similar to that of the spinal stichochromes.

The Sympathetic Ganglion Cell.

The knowledge of the structure of the sympathetic ganglion cell has been contributed largely by Kolliker,[65] Cajal,[66] Retzius,[67] Sala,[68] Dogiel,[69] Vas,[70] and Dehler.[71] These studies refer only in part to the structure of the chromatic portion of the cell.

Vas finds that chromatic substance is absent from the cell in the seven-months fœtus, and that it makes its appearance about the ninth month. At 11–12 years the sympathetic ganglion cell attains its full development, having greatly increased in size and in content of chromatic substance.

Dehler's studies refer to the sympathetic ganglion cells of the frog. These cells measure on the average 10 to 40 μ in diameter and present a great variety of forms determined by pressure of the rather dense connective tissue capsule of the ganglion in which they lie. They are surrounded by an endothelial sheath similar to that of the spinal ganglion cells. The chromatic substance appears in the form of granules or larger spindle-shaped masses, most abundant in the periphery of the cell and arranged concentrically, not about the nucleus, but around a certain point of the cell, or centrosome, which lies midway between the nucleus and the opposite pole of the cell. The large chromatic bodies lie at the periphery of the concentric rings and the finer granules at the centre. The nucleus may be encircled by one or more rows of large chromatic masses. In the centrosome are to be found a group of granular chromatic bodies staining deep black by Heidenhain's hematoxylin.

Dehler follows the technical methods of Flemming, tracing fine fibrils entering the cell from the processes, but does not find that they are connected with the nucleus.

The spiral fibres encircling the bodies of the sympathetic ganglion cells are not demonstrable by Nissl's method. The nuclei of the sympathetic ganglion cells are similar in all respects to those of the spinal ganglion cells. In most of the higher vertebrates, especially in young individuals, double nuclei are frequently seen in these cells. Small chromatophilic cells are rather abundant in sympathetic ganglia.

Dogiel employed the method of vital injection of methylene blue and his investigations were principally devoted to the course and relation of fibres and intracellular fibrils.

According to Dogiel the chromatic masses are usually of moderate size, of oval or angular form, and stain with varying intensity by Dogiel's vital injection method. They are more numerous in central areas, sometimes project beyond the cell borders, are seen in dendrites and even in the crescentic area of origin of the axis cylinder process. By high powers these masses are seen to be composed of fine granules. The intermediate substance is for the most part unstained by methylene blue, but in it are seen a network of fine fibres.

He finds a clear acidophile substance or groundwork about the dendrites and periphery of the cell body, similar to that in the axis cylinder process, and believes that the acidophile substance of the axis cylinder process and dendrites is continuous, running through the deeply stained portion of the cell.

The Structure of Purkinje's Cells.

According to Nissl these cells furnish the type of archystichochromes, their chromatic substance existing partly as large spindle-shaped masses, largest and most

abundant about the periphery of the cell and encircling the nucleus, and partly also in the form of a fine network found throughout the cell body, but most evident near the origin of the dendrites. There seems to be considerable variation in the number and size of the chromatic masses of Purkinje's cells in apparently normal cases. In some of the writer's specimens these bodies appear as densely packed as, though rather smaller than, in the spinal stichochromes. The dendrites of Purkinje's cells contain comparatively few chromatic spindles, but at the bifurcation of processes, even to the third or fourth order, a group of small chromatic granules may sometimes be detected. The presence of several small vacuoles, or as seems more probable, of small highly refractive translucent achromatic bodies, sometimes seen in the spinal stichochromes, is in the writer's specimens, a specially prominent characteristic of the nucleoli of Purkinje's cells.

The writer's sketch of a normal Purkinje's cell was made from a teased specimen dried and stained on a glass slide. The chromatic network and relation of chromatic bodies appear more distinct than in stained sections. (See Plate I, Fig. 2).

Structure of Cerebral Cortical Cells.

The majority of the smaller pyramidal cells of the cerebral cortex belong to the type of pure archyochromes, the chromatic substance being in the form of a fine network of granules, the meshes of which vary considerably in size. This network is traceable for some distance into the larger processes. In some cells the network is distinctly thickened at nodal points, a feature that becomes so pronounced in the deeper layers as to place some of the medium sized pyramidal cells in the class of archystichochromes.

The large ganglionic cells of the motor areas belong to the type of stichochromes, the chromatic bodies being numerous and distinct. The size and number of chromatic spindles in the dendrites is distinctly less in all cortical cells than in the spinal stichochromes.

The Medullary Nuclei.

The *locus ceruleus* and *substantia nigra* are composed largely of medium sized or large stichochromes in which are usually abundant masses of large pigment granules. When the deposit is moderate in amount the outline of the pigmented area may be distinctly marked off from the cytoplasm, in other cases the pigment is very abundant and distributed all through the cytoplasm, being thickly packed between the chromatic bodies.

Throughout the gray matter of the floor of the fourth ventricle and along its walls, the predominating type of cell is unquestionably the stichochrome, but in addition to this type one meets constantly with cells of a different constitution, often apparently belonging to the cranial nerve nuclei. Many of them are, undoubtedly, archystichochromes. Van Gehuchten[31] (p. 237) also depicts such cells in the nucleus of origin the *motor oculi* of the rabbit. The fact that the eighth nucleus contains largely typical stichochromes is hardly in accord with the theory of Nissl's classification, as noted by Van Gehuchten, who suggests that these cells may be cells of origin for the *post. long. fasciculus*, (p. 241, loc. cit.)

The cells of the *olivary bodies* belong to the class of archystichochromes, the chromatic reticulum being rather coarse and nodal thickenings distinct. At an early period, usually before puberty, a considerable area of these cells is converted into an achromatic, highly refractive, slightly

yellowish substance, much resembling the pigmented areas found in many cells and in which the persisting chromatic reticulum is usually very distinct.

The cells of the *external arcuate nucleus* are of the type of archystichochromes, with rather delicate reticulum and large chromatic bodies.

In the *upper medulla* the writer has met with a type of cell which has as yet escaped description, and of which a short reference may here be inserted. These cells are located externally to and above the *locus ceruleus*. They measure 40 to 70 μ in diameter, and are multipolar. They are very rich in chromatic substance, the structure of which constitutes the characteristic feature of the cell. Chromatic bodies are wanting, this substance being found in the form of a network of which the meshes are extremely coarse and thick. The appearance of these cells is totally different from that of any other type seen in the human subject.

At the same level of the medulla single or isolated groups of cells are found, which are identical in structure with those of the spinal ganglia.

An exhaustive study of the normal histology of the cells of the medullary nuclei is a contribution urgently needed, before detailed pathological studies can be conducted with advantage.

During the examination of the central nervous system of a child, seven years of age, dying from shock and hemorrhage, a number of interesting cytological features were observed which are probably characteristic of early life.

The groups of cells in the medulla were much more compact than in the adult. Often four or five cells in

section lay in immediate contact with each other, and some of these cells were distinctly united by broad processes. The chromatic bodies of the large stichochromes were large and extremely abundant. Different types of chromatic structure were more distinct than in the adult, and some groups of cells in the medulla which the writer has never encountered in the adult, presented the structure of the sympathetic ganglion cells.

In new born infants, many of the above peculiarities were noted, but the chromatic bodies at this period were usually very deficient in size and number. The chromatic masses of Purkinje's cells at birth appear to be, as a rule, extremely small and faint.

Babes[72] finds that the "Nissl bodies" are often limited to the perinuclear region, in the normal infant.

Vas[70] has found that the chromatic bodies are wanting in the sympathetic ganglion cells at the seventh month of fœtal life, that they make their appearance in the form of small granules at the ninth month, and are not fully developed until the eleventh year.

Eve[73] also notes the absence of chromatic bodies in the ganglion cells in early fœtal life in the rabbit, finding that only the vagi nuclei in the embryo 2.5 c.m. long contain distinct masses of chromatic substance.

It falls without the scope of the present study to consider further these details of the histology of the medullary and higher ganglionic cells, but it is obvious that until a systematic study of this subject has been contributed, it must remain impossible to accurately interpret the variety of pathological appearances presented by the medullary nerve cells in early life.

Section III.

Physiological Condition of Ganglion Cells in the Central Nervous System.

Considering the great variety of appearances of the chromatic structure of ganglion cells demonstrated by Nissl's method, it is obviously important to know what digressions from the typical and normal aspect of these cells may be expected in the cord and brain of the average normal case.

It is by no means easy to secure at post-mortem material from human subjects in which a fatal lesion has not seriously involved the central nervous system.

The following cases are believed to partially meet these requirements:

Case I.—*Multiple Injuries, Hemorrhage, Shock.*—Male, 14 years; previously healthy. Was struck by a locomotive, receiving internal injuries from which death resulted in three hours, from shock and hemorrage. There was no elevation of temperature, and the patient was conscious until a few moments before death.

Autopsy six hours after death. The body of the first lumbar vertebra, the ramus and body of pubes, were fractured, and the tissues in each locality lacerated and infiltrated with blood. There were a few ounces of bloody fluid in the peritoneal cavity. The viscera were normal.

Microscopical examination. Van Gehuchten's fluid.

The *lumbar cord* was lacerated at the point of fracture and infiltrated with blood for some distance above and could not be used for the present purpose.

In the *cervical cord* the great majority of cells presented an abundance of well-formed compact chromatic masses. The chromatic network connecting these bodies was usually distinct. The nuclei and nucleoli were normal and centrally placed.

In *Clarke's column*, one large cell presented marked central chromatolysis and eccentricity of nucleus. All other cells in several sections were normal.

Immediately external to Clarke's column was a group of medium sized cells, seen in several sections, in which the

perinuclear chromatic masses were moderately subdivided and the nuclei eccentric.

In the *medulla* the majority of cells were perfectly normal in appearance, but it was possible in nearly every section to find some abnormalities.

All the cells of the nuc. XII, appeared normal. Above this nucleus nearly all the larger stichochromes also appeared normal, although the chromatic bodies were very large and of irregular contour. On the other hand, in many of the smaller stichochromes, and in the cells of the other mixed types which are abundant in this region, a moderate subdivision of perinuclear chromatic masses was the rule. A considerable number of examples was seen of central chromatolysis with eccentricity of nucleus.

Throughout the cortex, the appearance of the cells was more uniform. The chromatic bodies were almost invariably compact and regular. Sometimes they were deficient or subdivided in the perinuclear zone. In the archyochromes, attention was drawn to marked variation in the size of the meshes of the chromatic reticulum.

Purkinje's cells were rich in chromatic bodies of rather small size and somewhat indistinct contour.

The results of the examination of this instance were disappointing in the attempt to secure a case showing perfectly normal conditions throughout the central nervous system, and the lesions found must be referred to the severe concussion of the injury, and to the fatal shock and hemorrhage following it.

Barring the slight distortion of the chromatic bodies most evident in the medulla, and the changes in the single group of spinal cells, for which no explanation can be offered, the conditions found indicate a high development and uniform preservation of the chromatic structures in all regions, and to this extent the case serves its original purpose, indicating the physiological condition of the nervous system, in the young normal subject.

Case II.—*Dislocation of Cervical Vertebræ.*—Male, 60 years; fell four stories through an elevator shaft and sustained various injuries. Brought to hospital unconscious, but soon became rational, although there were intervals of mild delirium during the night. There was a fracture of the right femur, and complete hemiplegia below the clavicles. The next morning the patient was entirely rational, and asserted that he felt comfortable. It was noticed that he turned his head to one side, immediately after which he was found dead. Temperature 101.4°.

Autopsy eight hours after death.

There was a reduced dislocation of the third cervical vertebra and the cord at this point was crushed. There was a little fresh blood in the spinal canal and the cervical muscles were infiltrated with blood. The brain and medulla appeared normal. There was a very little extravasated blood in the gray matter of the cord, on either side of the crushed area. The viscera could not be examined.

Microscopical examination. Formalin 10 per cent.

In the *cord*, above the injured segments, the majority of cells showed extensive central chromatolysis, but many of the large stichochromes were intact. In a few cells "axonal degeneration" was noted.

In the *medulla*, the cells of the *XII nuc.* were perfectly normal. In the cells of the superficial *X nuc.*, there was an extensive deposit of yellowish granular pigment, but the remaining chromatic bodies were of normal appearance. The large stichochromes in the region of the *nuc. ambiguus* were intact.

In the *VIII nucleus* nearly all the cells were extensively altered, the chromatic bodies being limited to the periphery, the perinuclear areas being occupied by finely subdivided and partly faded chromatic particles. The nuclei were often eccentric, and pigmentation was excessive.

Apart from excessive pigmentation, and the resulting loss and displacement of chromatic bodies, no changes were noted in the *III, IV, V, VI and VII cranial nuclei.*

In a considerable number of deeper lying cells, in many groups not certainly identified with named nuclei, there was a moderate loss of perinuclear chromatic bodies.

In the *motor cortex*, the giant stichochromes showed extensive pigment deposits, but no changes in the chromatic bodies. In the smaller cells throughout the cortex, the perinuclear areas were often deficient in chromatic substance, and showed an early stage of pigment formation. Elsewhere the chromatic structures were intact. *Purkinje's cells* contained an abundance of chromatic bodies of somewhat smaller size than is usual. A very few of these cells were distinctly deficient in chromatic bodies.

With the exceptions of the extensive pigment deposits, and of the distinct changes in the *nuc. VIII*, which latter the writer is unable to explain, the chromatic structures of the medullary and cortical cells were found in nearly normal condition, and the case appears to furnish a normal standard of comparison for subjects of this age.

Some experimental studies may here be cited on the effects of traumatism and shock on the nerve cells.

After inflicting a severe blow on the abdomen of rabbits, a traumatism proving fatal in from four hours to four days, Parascandolo[74] found by Golgi's method a shrinkage of the cells and rupture of processes; by Marchi's method, degeneration of fibres of Lissauer's column, of the posterior roots, and often of the posterior tracts; by Nissl's method, a considerable variety of forms of chromatolysis. Vacuolation was frequent, but any nuclear changes seen were of uncertain character. He thinks these cellular changes will explain many of the symptoms seen in shock from such injuries.

Luzenberger[75] describes a peculiar concentration of the chromatic substance at one pole of the cortical cell in animals killed by blows on the head. This lesion was limited to the areas most exposed to the traumatism.

The observations of Babes[72] also indicate that in the nervous system of the average adult subject the permanent effects of previous diseases may be found in the presence of a moderate number of altered cells. Clarke's column, the lateral portions of the anterior horns, and some medullary nuclei, he indicates as the regions most often containing such abnormal cells. In aged subjects he rather frequently finds cells that have lost their chromatic bodies, or have become atrophic, as well as those exhibiting extensive deposits of pigment. In young subjects with sound organs, such appearances are much rarer. In animals recovering from various infections he found, after several weeks, many more altered cells in the anterior horns than in control animals.

Section IV.

On Cadaveric Changes in Ganglion Cells.

The writer in sudying the pathological changes in nerve cells in various diseases, was early impressed with the frequency of alteration, which was most naturally referable to post-mortem processes, and being unable to find at that time (1895) any adequate discussion of this branch of the subject, was compelled to make a preliminary study of cadaveric changes in the ganglion cell as demonstrated by Nissl's method. All that has been said in reference to the artifacts produced by fixing agents, is of course of equal import in connection with post-mortem changes. In the writer's experience it has often been impossible to distinguish the one from the other, principally when dealing with vacuolation and the chromatophilic condition.

The course of post-mortem changes in the ganglion cell as revealed by previous methods has been rather imperfectly described by several observers, and among these studies may be mentioned that of Schulz.[76] Recently several studies on post-mortem alterations of the chromatic substance of nerve cells have appeared. Colucci[77] has considered in detail the cadaveric changes demonstrated by Nissl's method. He finds that while adult nervous tissue undergoes post-mortem changes more slowly than most other tissue, yet it does not, even under favorable conditions, enjoy freedom from cadaveric alteration longer than twenty hours. The dependent portions, especially the second and third temporal convolutions and the cerebellum are the first regions to lose consistency. Microscopically, cadaveric changes consist principally in:

First.—Granular disintegration of the cell body, giving it a powdery aspect, or leaving it homogeneous and

diffusely stained. All the elements of the cell are involved in this change, last of all the nucleus, and its prominent characteristic is the uniform involvement of the entire cell body with alterations in the form of the cell. Very early and characteristic changes are to be noticed in the second and fourth layers of cortical cells, while the larger pyramidal cells of the cortex and medulla are more resistant. The fibrillar or achromatic portion of the cell is more apt to show these changes than are the chromatic bodies.

Second.—Colucci notes that various segments of the processes are apt to remain unstained and thus give a false appearance of fragmentation of these processes.

Third.—Complete rupture of processes in various directions may occur in the course of cadaveric alteration.

Fourth.—Black droplets may be demonstrated by Marchi's method, either in the processes or in the cell body, or the entire cell may appear jet black, as the result of post mortem changes.

Neppi[78] noted the course of cadaveric alteration in the spinal stichochromes of the dog. Within six hours after death he found these cells in normal condition. A faint areola about the nucleus was noted, the significance of which appeared uncertain. After 24 hours the chromatic substance appeared normal, but in some cells a slight nuclear chromatophilia was observed. After 48 hours there was a diffuse staining of the entire cell body, but the chromatic bodies appear well differentiated, although often very scarce in the protoplasmic processes. The outlines of the nucleus are less regular, and the karyoplasm shows a light diffuse bluish stain. The nucleus may become eccentric. After 72 hours the changes of the last stage are moderately increased. After 96 hours the cell

outlines are more ragged, the chromatic masses are very scarce in the processes, and in the cell body they stain very faintly. Sometimes the dark areola about the nucleus is much increased in extent. The outlines of the nucleus are irregular and indefinable.

In general, Neppi finds that cadaveric processes lead to a gradual disintegration and fading of the chromatic bodies, accompanied by a shrinkage and chromatophilia of the nucleus. This cadaveric chromatolysis does not, in his opinion, greatly resemble the vital chromatolysis described in various pathological conditions. As the initial alteration he regards of first importance the diffuse staining of the karyoplasm. The irregularity in outline of the nucleus and the shrinkage of the cell body are the most reliable indices of post-mortem as distinguished from vital pathological alterations.

Barbacci and Campacci[79] report a systematic study of cadaveric changes in various parts of the nervous system of rabbits. They used the methods of Nissl, Golgi, and Marchi. Nissl's method revealed, as the initial change, a diminution in the staining capacity of the chromatophilic masses. This change is associated with an irregularity of these bodies, their borders becoming indistinct, and two or more often appearing to be fused together in a larger mass, or the bodies appear to be broken into irregular particles. Occasionally the peripheral masses are entirely bleached, while the perinuclear bodies remain intact. Small areas or the entire cell body are sometimes found homogeneous and deeply chromatophilic.

The granular disintegration of the chromatic masses often gives the cell body a characteristic pulverulent aspect. Vacuoles of various sizes are often seen especially when the protoplasm appears homogeneous. Very

frequently the protoplasm shows a characteristic reticular aspect, the meshes of the reticulum being of varying size and the threads coarsely granular. The irregularity in the size and shape of the meshes of this reticulum serves to distinguish this change from the vital and pathological formation of vacuoles which latter are always rounded and sharply limited. The authors believe that it is quite possible to mistake the initial stages of putrefactive changes for the peripheral chromatolysis so often attributed to pathological processes.

The *nuclei* are sometimes found irregular in outline, sometimes swollen and homogeneous, but with very distinct outlines. The intranuclear network is converted into a series of irregularly placed granules. In advanced stages the nucleus becomes shrunken, ragged, and often homogeneous and deeply stained. In very advanced stages of decomposition the nucleus is indistinguishable, although the nucleolus usually persists in some form. Alterations of the *nucleolus* are relatively late, in cadaveric processes, as observed by these authors. They consist chiefly in eccentricity or extrusion of the nucleolus, in various changes in its form, and, at advanced stages, in swelling and fragmentation. In all these phases there is a progressive loss of staining capacity. In Golgi's method the author describes principally a peculiar irregularity or erosion of protoplasmic processes, which they term the "stato torlato," and which they find to have no resemblance whatever to the varicose atrophy or moniliform condition now generally regarded as of pathological import. The full report of their observations is to appear later.

Levi[80] finds that the first cadaveric changes appear in the cortical cells within 18 to 24 hours after death, in the

spinal ganglia within 36 to 48 hours, and in the cord within 60 hours.

The cells first appear coarsely granular and more intensely stained than usual, while the nuclear membrane becomes indistinct. After this "hyperchromatic stage" the cell body takes on a violet tinge with methylene blue, becomes irregular in outline, while the nucleus loses its identity, the nucleolus only being distinguisable. His studies were upon the central nervous system of rabbits, removed after killing the animals by bleeding, and exposed to the air.

The writer's observations on cadaveric changes in ganglion cells consist in the examination of the brains and cords of rabbits in successive stages of decomposition, and in the study of alterations noted in cases coming to the autopsy table in from one to forty-eight hours after death.

In the course of these observations, the ordinary rules governing the course of post-mortem changes in the cadaver were found to be fully illustrated. In warm, moist weather, advanced decomposition of the central nervous system was found in some cases within six to eight hours, while in the coldest winter weather, the tissues were apparently intact in the great majority of instances after 24 hours. The condition of the tissues before death as determined by the nature of terminal infections proved of very great influence on the rapidity of change immediately after death. Cases of septicæmia, pyæmia, peritonitis, and the infectious diseases, seemed to require that the tissues should be removed and placed in preservative fluids within two to four hours, if one hoped to avoid serious alterations in the finer structure of the cells. In a case of leukæmia terminating in infection by the *bacillus*

aerogenes capsulatus, the most bizarre phases of post-mortem destruction, predominated by gas formation, were found in the brain and cord, although the autopsy was held in January, eight hours after death.

It does not appear possible to state for all conditions any approximate period within which the cellular structure demonstrable by Nissl's stain may be affected by post-mortem alterations.

As a rule, the writer would regard with suspicion any areas showing simply granular disintegration of the chromatic bodies and nuclear chromatophilia, the earliest post-mortem alterations, unless the tissues had been preserved within four to six hours, or in septic cases within two hours after death. In the brains of very young infants the change proceeds with surprising rapidity.

After removal from the body, the brain and cord may be preserved without noticeable change for 26 to 48 hours longer, if kept in cold storage at 32° C. After four days' storage in this way, the brain from a case of eclampsia, showed only a slight increase in the diffuse staining of the nuclei and a slight dimness in outline of the cell body and chromatic masses, which could be referred to cadaveric processes.

A series of observations undertaken for the study of post-mortem changes in the nerve cell consisted in the examination of the central nervous system of rabbits, which had been allowed to decompose in the air for from 48 to 72 hours. Under these conditions the changes seemed to follow a somewhat uniform course. The alterations observed appeared to fall into three distinct periods.

The changes of the *first period* were well marked within 24 hours, and were characterized chiefly by a granular disintegration of the chromatic substance. This alteration

was most uniform and general in the cortical archyochromes which at this time showed an irregular network of larger, more distinct, deeply stained granules, replacing the normal fine granular chromatic network. The achromatic substance at this stage appeared slightly clouded or displaced by vacuoles. The outlines of the cells remained intact. In the spinal stichochromes the outlines of the chromatic bodies were slightly irregular and indistinct and the granules larger. (Bichloride fixation). In the dendrites there was an irregular network of fine granules, and the chromatic spindles appeared more coarsely granular than in the fresh specimens treated by the same methods.

In many instances the nuclei of the cortical cells showed a tendency to stain diffusely but this change was not pronounced.

Characteristic changes early affect the nucleus. The first indication of post-mortem alteration of the nucleus is seen in a progressive clouding of the intranuclear network. This change usually begins about the nucleolus, of which the chromatin appears to diffuse along the intranuclear network producing a diffuse chromatophilia immediately around the nucleolus and extending a variable distance out toward the nuclear membrane. Plate III, Figs. 1–2.

When decomposition is rapid all parts of the nuclear network may be simultaneously affected, and appear uniformly thickened and coarsely granular. Plate III, Fig. 3.

In the *second period*, usually well marked at the end of 48 hours, the characteristic feature was the uniform clouding of the nuclei of the cortical archyochromes. After 24 hours the outer zones of these nuclei were usually clear and retained their delicate intranuclear network. In the second period, the intranuclear network was no longer

visible, and the nuclei almost without exception, appeared evenly and diffusely stained throughout. The nucleolus were sometimes almost invisible. This diffuse nuclear chromatophilia appears to spread from the nucleolus outward, as in many of the larger and less affected cells, nuclei were found showing all transitions from a narrow radiating chromatophilic zone about the nucleolus, characteristic of the first stage, to a dark discoloration of the entire nucleus.

The granular disintegration of the chromatic substance advanced rapidly in this stage, especially in the archyochromes. The normal network was now replaced by an irregular deposit of large discreet granules, often partially grouped, and usually leaving a clear zone about the discolored nucleus. In many cells large and small clear vacuoles appeared, distorting the outlines of the cell body, and disturbing the position of the large granules. In the achromatic substance an increasing chromatophilic tendency was constantly noted.

A characteristic change also belonging in its earlier stages to this period, was observed in the shrinkage of the dendrites which now became irregular in outline and staining qualities, and often followed a wavy or spiral course through the section.

In the spinal stichochromes the nuclear changes were less marked, but the diffuse staining of the achromatic portion of the cell body and dendrites and the irregularity and coarse granulation of the chromatic bodies exceeded those of the first period. In some instances the granular disintegration of the chromatic structures proceeded much more rapidly and at the end of 24 to 36 hours the cell body presented an irregular network of large granules unevenly distributed over the cell

and often found free in the pericellular lymph space. Plate III, Fig. 3.

The *third period* was characterized by the growth of putrefactive bacteria in the finer capillaries and in the pericellular lymph spaces, by the disintegration of the cell body, and by the separation of dendrites.

When bacteria begin to develop in the vicinity, the outlines of the ganglion cells soon become irregular and broken. The perinuclear zone of vacuoles fuses with the large peripheral vacuoles, and these open into the pericellular lymph space often leaving the border of the cell to be indicated only by a single row of dark granules. The process continues until nothing is left of the cell except a dark nucleus with a narrow fringe of dark granules. All stages of shrinkage, rupture, and complete destruction of processes may be followed at this period. The appearance of the nuclei is very characteristic. They are usually diffusely and very darkly stained. The nucleoli usually are much reduced in size but are often surrounded by such a deeply stained area that the central nucleolar spot becomes very indistinct. The nucleoli may also be numerously subdivided.

A striking difference noted in the spinal stichochromes was the resistance offered by the chromatic bodies of these cells to the effects of bacterial invasion. In some instances the cell body was riddled with bacilli and the pericellular lymph space choked with them, while the chromatic masses still retained a distinct outline, undiminished staining capacity, and showed only a moderate increase in the coarseness of their granules. Usually, however, the outlines of the chromatic bodies were irregular and indistinct, and often they were completely broken up into coarse, dark granules. Throughout these periods

the spinal cord proved more resistant to cadaveric decomposition than did the brain or medulla. The fact that Purkinje's cells followed closely the behavior of the other cortical cells rather than that of the anterior horn cells, indicates that the slower progress of change in the spinal cells is referable to local conditions under which these cells are found and not to structural differences. Possibly the smaller content in fluids and the more rapid dessication of the cord may account for some of these differences, yet they were well marked in specimens allowed to remain in the body, where dessication was impossible.

Comparing cadaveric changes found in cases coming to autopsy, under diseased conditions, with the course of post-mortem processes in normal rabbits, much less uniformity was observed.

Extreme differences were noted in the periods required for the development of cadaveric changes in the human subject, so that it is impossible to give any approximate number of hours within which the stages detailed above may be expected to appear. As before mentioned, the rapidity of the process depends upon the ordinary factors governing post-mortem changes, the most important of which seems to be the condition of blood and tissues at death, and next in importance the condition of the surrounding air.

It was often observed that a lack of uniformity existed in the character of the changes, both in different portions of the cerebro-spinal axis and in the nuclei of the same segment of the medulla. Central nuclei were sometimes found more affected by cadaveric processes than were superficial groups of cells.

Yet whatever period the changes might have reached it always seemed possible to distinguish with certainty between post-mortem and vital pathological processes, except when dealing with increased chromatophilia of the nuclei of cortical cells.

The writer has found no evidence indicating that cadaveric changes can simulate the characteristic central chromatolysis so often described as a part of pathological changes. No post-mortem appearances were encountered resembling the conditions seen after insolation. Even in the granular disintegration of chromatic bodies the cadaveric change is distinguishable from the pathological by the large size (bichloride fixation) and density of stain of the resulting granules, and by the uniform involvement of the entire cell.

In the spinal stichochromes of a rabbit dying soon after a subcutaneous injection of the poison of a *water-moccasin*, distortion and granular subdivision of the chromatic bodies was found closely resembling post-mortem disintegration, but distinguishable from it by other features in the cells and surrounding tissues.

In regard to nuclear chromatophilia, the author is inclined to believe that this particular cadaveric alteration is sometimes indistinguishable in itself from a pathological change sometimes observed. Recourse must then be had to evidence obtainable from the probable condition of the tissue and the other characters of the cells.

In this connection may be mentioned some artificial changes probably referable to the traumatism applied during the removal of the brain or cord from the body.

The layer of Purkinje cells may sometimes appear to be separated from the adjoining layer by a zone of tissue

similar to the molecular layer. The writer has found this condition very marked in specimens rather roughly extracted from the cranium and frequently handled, and has been unable to find it when the cerebellum was removed with extreme care and immediately hardened.

It seems probable, that the rupture of dendrites much more frequently results from similar traumatism than from pathological processes.

In some specimens, removed one hour after death, large radially striated or coarsely granular bodies staining densely blue, or sometimes purple, have been found, most abundantly in areas composed of nerve fibres but sometimes occupying the centres of large ganglion cells, distending the cell borders, pushing aside and compressing nuclei and chromatic bodies, or almost entirely obliterating all trace of the cell. These bodies have been described by some as droplets of myelin. They are more abundant in roughly handled tissues.

No evidence was found to indicate that the position of the nucleus is materially altered during the earlier stages of post-mortem decomposition. Later extensive vacuolation may lead to partial eccentricity of the nucleus.

Section V.

Pathological Changes in Chromatic Structures.

Having considered the technics of Nissl's method, the effects of reagents and of mechanical injury on the nerve cell, the normal histology of the ganglion cell in some regions, and the course and character of post-mortem changes, attention may now be turned to the pathological changes in the ganglion cell as demonstrated by this method.

A.—*On Changes in Ganglion Cells in Diseases of Nervous System.*

I.—*Neuritis and Lesions of Nerve Trunks.*—The early observations on pathological changes in ganglion cells revealed by Nissl's stain were largely limited to experimental lesions produced in animals, and it must be admitted that the more definite facts now known regarding the significance of certain changes in the chromatic bodies have been derived from experimental pathology.

Cellular Lesions Following Section of Nerve Trunks.—One line of experimentation rather fully studied has been the effects on the spinal cells of various lesions of their fibres. On this subject many previous investigators have described a variety of changes demonstrated by other methods, principally Marchi's, and leading in the most advanced stages to complete disappearance of the cell. These studies may be found reviewed in the article of Onufrowicz.[81]

Nissl[82] observed that characteristic changes could be induced in the cells of the facial nucleus by tearing out the facial nerve trunk in rabbits. Within 24 hours after this procedure he found that the chromatic bodies of the affected cell, began to disappear in a small area of the cell body. After two days the chromatic masses throughout the entire cell began to break up into a number of fine pale granules. By the third day the same changes affected the chromatic spindles in some of the dendrites, while the achromatic part of the cell began to darken. On the fourth day, he noted progressing disintegration of the chromatic bodies and swelling and irregularity of outline in the cell body. On the sixth day the cell body was rounded and presented a uniformly dusty appearance, while the dendrites were usually invisible. The

nucleus had now migrated to one side, often projecting beyond the cell. By the tenth day, the cells were reduced to irregular waxy-looking or slightly granular masses without nuclei or dendrites. These changes did not affect all the cells of the facial nucleus with equal rapidity, but, on the tenth day, all phases of the above alterations could be seen in different cells.

Without the knowledge of Nissl's work, Onufrowicz followed the changes in the spinal cord resulting from section of the dorsal nerve trunks in cats, considering chiefly later stages of degeneration found six days after the operation. His observations confirm those of Nissl. The anterior horn cells of the affected side and some also of the opposite side were found to be homogeneous, swollen, and entirely devoid of chromatc bodies, or showing only a little granular detritus. Somewhat simular changes with a marked tendency in one case toward chromatophilia were found in the cells of the posterior and lateral horns and in Clarke's column. The nuclei of the cells were often found markedly eccentric and in various stages of degeneration.

Marinesco[83] slightly varied the procedure of Nissl, simply cutting the nerve trunk and observing the changes in the cells of origin. He describes two phases of degeneration in the nerve cell induced by section of the efferent trunk. *First*, there is, according to Marinesco, a loss of chromatic bodies as described by Nissl, beginning about the axis-cylinder process, and effected, as he believes, by a process of hydration. He also noted the eccentricity of the nucleus. *Secondly*, he finds a disintegration of the protoplasm of the cell body indicated by changes in the achromatic substance.

Lugaro[84] studied the effects of transverse section of the

cord in rabbits, and found that all cells within two or three mm. above and below the point of section degenerated, and after a time disappeared. All the cells within four mm. of the point of section, except the anterior horn cells showed the characteristic chromatolysis with swelling and loss of processes as described by Nissl. He concludes, therefore, that the lesions of the cells are greater and earlier the more extensive the lesion of their processes. Lugaro also found that while section of the peripheral roots of the spinal ganglia induces changes which progress to the total destruction of the cell, section of the central roots usually leaves the cells in their normal condition.

Savdovsky[85] ligated the sciatic in rabbits and described the changes in the cells of origin present at the end of four to five days. These consisted in a loss of chromatic bodies at the periphery of the cell and atrophy of many of the angles, concentration of large chromatic masses about the nucleus, and eccentricity of the nucleus.

Flatau[86] also observed all grades of the lesions described by Nissl in the nuclei of origin of the oculo-motor nerve, after section of the nerve in cats.

Charrin and Thomas[87] found in the spinal cord of a guinea pig two months after a double amputation, the changes described by Nissl and others as resulting from section of nerves.

After section of the brachial plexus in rabbits Colenbrander[88] found extensive chromatolysis, eccentricity or loss of nucleus, loss of dendrites, and sometimes extreme swelling of the cell body.

Marinesco[89] verified the observations of Lugaro that section of the central roots of the spinal ganglia induced very slight changes in the cells of the ganglia, while the usual lesions rapidly followed sections of the peripheral root.

Marinesco has also studied the regenerative changes in the cells of the twelfth nucleus 24 days after section of the hypoglossus. At this period he finds that the cells are enlarged, that they stain very deeply from increase in the size of the chromatic bodies, that the nuclei remain eccentric, and that some cells become permanently atrophic. The new formation of chromatic bodies may begin in a central or peripheral ring or irregularly throughout the cell.

Flemming,[90] in an extended study by Nissl's method of the effects of section of nerve trunks on the cells of the spinal ganglia and cord, came to the following conclusions:

(1) The cells of the spinal ganglia are affected earlier (4th to 7th day) than are the anterior horn cells of the cord, but after the fourth week, the changes advance more rapidly in the cord than in the ganglia.

(2) One of the first changes is a shrinkage of the nucleus, often also of the nucleolus, and a lateral migration of the nucleus.

(3) The chromatic bodies first appear to be concentrated about the nucleus where they become reduced in size and number and break up into fine granules. Some remaining chromatic bodies may be increased in size.

The most comprehensive description of the changes in ganglion cells following section of nerve trunks is given in a summary by Van Gehuchten.[91] According to his observations the changes that follow in motor nerve cells affect the chromatic substance only, the underlying network remaining intact, the nucleus showing no degenerative characters, and the cell under favorable circumstances returning to its normal morphology. Such cells cannot be said to reach a condition of true degeneration.

When, however, the peripheral roots of spinal ganglia

are severed or ligated, the cells of these ganglia suffer changes affecting both the chromatic and achromatic substance, and the changes go on to complete degeneration. The reason for this difference in the behavior of motor and spinal ganglionic cells is found in the anatomical relations of the cells. After ligation of the filaments of motor cells the nutrition of these cells is maintained by the trophic influence of adjoining neurons. After ligation of the peripheral filaments of the spinal ganglia these cells, according to Van Gehuchten, are entirely cut off from exciting impulses and completely degenerate. (See also Flatau[86]).

It will be seen that there is not complete accord in the observations of Van Gehuchten and others, and that the facts observed do not fully bear out the very rational theories of Flatau and Van Gehuchten. Onuf and Marinesco describe true degenerative changes in motor cells after section of nerve trunks.

This entire subject requires complete readjustment on the basis of the more minute changes in the chromatic and achromatic structures following ligation of nerve trunks.

The writer's sections of pathological material indicate beyond doubt that long established neuritis affecting motor nerves leads to true degeneration and destruction of the anterior horn cells of the spinal cord. The changes in the achromatic substance and loss of dendrites do not always follow immediately upon the lesion of the fibre, as, in the case of alcoholic neuritis, reported in detail later, the chromatic bodies were largely destroyed in some cells which still retained their cyto-reticulum. In others it was evident that all portions of the cell were affected, the

normal cyto-reticulum was wanting, the achromatic substance was coarsely granular, and the processes were shriveled or absent.

It seems probable that the conclusions now warranted in reference to this subject are that after section of nerve trunks, some cells of origin proceed at once to degenerate and disappear, others merely lose their chromatic substance for a time either to recover or later to pass into a further stage of degeneration. The determining influence in the fate of the cell may very well be the trophic impulses enjoyed by the cell, and the partial preservation of function.

Origin of Changes Following Section of Nerve Trunks.— The results of section of nerve trunks on their cells of origin raises several questions of importance in the physiology and pathology of the ganglion cell. One very natural inquiry relates to the chain of events that leads to these alterations in the anterior horn cells after section of the anterior nerve roots. A more difficult problem is encountered when one endeavors to explain the absence of changes in the spinal ganglia after section of their central roots. Why should section of the peripheral roots of these ganglia induce lesions which are entirely absent after section of the central roots?

Since any direct traumatism to the ganglion cell can hardly be assumed to follow section of nerve trunks, it is necessary to assume that the cellular changes result from a disturbance in the physiological functions of the cell. On this assumption there is not only good reason for accepting the belief in the unity of ganglion cell and peripheral process as embodied in the modern conception of the neuron, but there is also a full explanation of the changes observed in the anterior horn cells after section of

the anterior nerve roots. Such a lesion of the roots by destroying the activity of the cell leads rapidly to changes in the nutrition of the cell which may, in the event of the lesion becoming permanent, progress to complete atrophy. A similar explanation applies to the restoration of the chromatic bodies after the physiological functions of the cell have been restored by union of the divided trunk, as observed by Savdovsky, Marinesco, etc.

In the experiments of Lugaro, after a transverse section of the cord, no changes were found in the ganglion cells below this lesion, except throughout a narrow segment adjacent to the lesion. It would, therefore, appear that the voluntary control of the functions of the anterior horn cells may be inhibited without inducing morphological changes in these cells.

Flatau, in discussing this subject, refers the absence of changes in such conditions to the continuance of the reflex activity of the cell, which of course is not annulled after section of the cord. It then appears that the persistence of reflex activity and presence of peripheral excitation are of greater importance in maintaining the normal nutrition or at least the normal morphology of the cell than is the excitation by voluntary impulses.

It is also possible to suppose that the continued excitation reaching the ganglionic cells through the peripheral roots is sufficient to maintain their nutrition even after section of their central roots, while, on the other hand, section of the peripheral roots leads to atrophy.

A second question of importance is the pathology of the nerve cell here presents itself. Since characteristic changes in the ganglion cells consisting principally in central chromatolysis and eccentricity of nucleus have been found to follow the section of nerve trunks, and the loss

of functional activity in the cell, *is it safe to infer when these characteristic changes are found in ganglion cells that these cells are no longer functionally active?* That such an inference is justified appears very probable from the result of the experiments detailed above. As will be seen later, however, similar lesions of very irregular distribution may be observed in many fatal general diseases, especially of the infectious type, and it is quite possible that other influences not interfering with the conductivity of peripheral nerve fibres may be capable of producing these lesions. A careful study of the conditions under which such typical lesions have been observed by the writer, has furnished no evidence against the view that cells in this condition are no longer functionally active. The further evidence on this point may be derived from the consideration of cellular changes in various other pathological conditions to be described later.

A third important bearing of this series of experimental studies concerns *the relation of cellular changes in the spinal ganglia and gray matter to peripheral neuritis*, especially in alcoholic and diphtheritic cases.

Before the publication of Nissl's method, many writers had described central cellular lesions in peripheral neuritis. (See Ballet[92]). One of the first observations on such lesions demonstrated by Nissl's method was reported by Ballet and Dutil[93] in a case of fatal peripheral neuritis in which the usual appearances of "axonal degeneration" were found in the spinal stichochromes.

Soon after, Marinesco[94] reported a similar case which he had examined some time previously and found central chromatolysis in the spinal stichochromes. In a second case of polyneuritis with lesions in the cord, reported by Marinesco,[95] central chromatolysis was found in the cells

of the postero-external group of cells in the lumbar region, while the achromatic substance remained normal.

The writer's series includes one case of fatal alcoholic neuritis in which advanced and very characteristic lesions were found in the central nervous system.

The patient gave no previous history of disease. Had long been a hard drinker of beer and whiskey. Two months before admission to hospital, he began to have dull pains in both knees, calves, and ankles, followed in a few weeks by difficulty in walking, incapacitating him from work. The paralysis became complete and soon extended to both forearms. There were numbness and tenderness in the extremities but no pain. The knee-jerks were lost. The muscles of the arms reacted to faradism. The muscles of the right leg reacted slightly, those of the left, not at all to faradism. Three days after admission, there was paralysis of the diaphragm, double external strabismus, rigidity of neck and mild delirium. Without any rise in temperature the patient died. Autopsy by Dr. F. C. Wood, to whom the writer is indebted for the material from the case. There were no gross visceral lesions of importance.

Microscopical examination. Alcohol, 95 per cent.

Throughout the *lumbar cord*, the anterior horn cells showed in advanced degree all the changes described as following section of nerve trunks. Nearly every cell showed marked central or complete chromatolysis, with eccentricity of nucleus. Many of these cells had passed beyond this stage, and were entirely lacking in normal characters, containing no traces of chromatic substance and both cell body and nucleus appearing greatly shrunken.

The earlier stages of the same lesions were found in the *cervical cord*.

Throughout the *cranial nerve nuclei* the majority of the cells showed central or complete chromatolysis with eccentricity or protrusion of nuclei. Many of the cells in some nuclei however appeared quite normal. The *nucleus X* and *nucleus ambiguus* were extensively altered.

The cells of the *cortex* and *cerebellum* showed only slight fading of chromatic bodies or appeared quite normal.

The microscopical lesions in the central nervous system

in this case seem to accord in all essential particulars with the clinical history. The affection of the lower limbs was of long standing (2 mos.) and the shrinkage and loss of processes in the cells of the lumbar cord were the evidences of a rather old established lesion. The upper extremities were more recently affected and few of the shrunken cells were seen in the cervical enlargement, although many showed an advanced stage of the usual change.

Respiration and the special senses were affected shortly before death, and in the medulla only the earlier stages of cellular alteration were to be found.

Opposed to these positive results, are the reports of some cases of neuritis in which the microscopical examination failed to show cellular lesions to account for the clinical conditions.

Not much significance can be attached to the report by Courmont,[96] of a case of probable neuritis in a rabbit in which no lesions were found in the cells of the spinal cord. The animal died with paraplegia four days after an intravenous injection of a culture of the cholera bacillus.

Dejerine and Thomas,[97] report a case of alcoholic neuritis with paralysis in which the motor cells of the cord were found to be normal. Three years before death the patient suffered from complete paralysis of all extremities, but had gradually improved until motor power in the arms was normal, while the legs remained paralyzed. Nissl's stain showed no changes in the cells of the cord or medulla. This is an important case, but it appears to stand alone.

Soukharoff[98] also reports a case of undoubted toxic neuritis, in which he was unable to find any changes in the motor cells of the cord.

Carriere,[99] reports an absence of cellular lesions of the cord in two cases of peripheral neuritis, in tuberculous subjects, but the importance of his observations is lessened by the incomplete loss of function in the cases, and by the irregular distribution of the clinical lesions presented.

The negative results reported in at least two of the above cases require that there should be further observations in this department before it can be positively stated with what frequency and extent central cellular lesions may be expected in cases of peripheral neuritis. It seems reasonable to insist that no case should be accepted as showing no central lesions if only isolated groups of muscles are affected, or if every segment of the cord and medulla has not been submitted to the microscopical test.

The weight of evidence seems to be strongly in favor of the belief that every case of established peripheral neuritis is associated with cellular changes in the spinal cord.

Primary vs. Secondary Lesions of the Nerve Cell.—An interesting question developed by the study of central lesions in neuritis relates to the difference between primary and secondary lesions in the nerve cells.

Marinesco[100] was one of the first to note that the central cellular lesions in peripheral neuritis are similar to, though not quite identical with those following section of nerve roots. In one of his communications, he endeavors to distinguish between primary and secondary lesions of this type in the ganglion cell.

When the cell is primarily affected, as after ligature of the aorta, or in Landry's paralysis, Marinesco finds that chromatolysis begins at the periphery of the cell, the nucleus remains central and the achromatic substance

early shows changes such as vacuolation and rupture of processes. In secondary changes, as after section of nerve trunks, there follows partial or complete perinuclear chromatolysis, the nuclei migrate to the periphery, and the dendrites are not broken although their chromatic spindles are reduced in size and number.

The writer cannot find that this plan of distinction between primary and secondary lesions of the nerve cell has been received with much favor. Ballet[92] in discussing Marinesco's and other views and reporting a case of central cellular lesions in beriberi, finds himself unable to state whether the cellular changes of peripheral neuritis are primary or secondary, since the lesions do not follow one type.

Charcot, Marie, Raymond, and Babinski, (quoted by Marinesco) all believe that all polyneuritis depends on a primary lesion of the nerve cell.

Colucci[77] in an exhaustive discussion of pathological changes in ganglion cells demonstrated by various methods, is unable to distinguish between primary and secondary lesions. He finds great similarity between the primary lesions in Landry's paralysis, etc., and those induced by section of nerve trunks. Commenting on Marinesco's views, he concludes that the peculiarities of primary and secondary lesions as described by Marinesco indicate only variations in the resistance of the different elements of the cell, and depend upon the acuteness or chronicity of the morbid process, but do not show distinctly any differences distinguishing a primary and a secondary origin.

The writer's observations on a considerable variety of conditions, support the conclusion of Colucci. The changes described by Marinesco as secondary are certainly

found in the great majority of altered cells in the general toxæmia of the infectious diseases.

That a morphological distinction between primary and secondary lesions should exist seems to be a reasonable expectation, but further studies are needed before it can be demonstrated.

II.—*Myelitis.*—Friedmann's[101] well-known researches on the cellular lesions of acute exudative encephalitis and myelitis were among the first applications of Nissl's method to general pathology, and did much to bring the method into general prominence. After reviewing the scheme of degenerative changes in the ganglion cell, given by Meynert in 1868, Friedmann notes the distinct additions to the knowledge of the subject furnished by Nissl's method.

On the second day of the myelitic process, Friedmann found some cells in an advanced stage of chromatolysis, which he calls "homogeneous swelling." This process, he concluded, begins at the centre of the cell and gradually destroys all chromatic bodies. The dendrites and nuclei are often in good condition when the entire cell body is swollen and homogeneous, but later, the dendritic spindles fade, the nuclear outlines become irregular and indefinite and the nucleolus becomes divided. Another variety of lesion which he regarded as distinct from though often associated with simple chromatolysis, he denominates as "granular (molecular) or fatty degeneration." In this process the chromatic bodies first break up into fine, deeply staining granules, which later lose their affinity for methylene blue, undergo a fatty transformation, and the cell is reduced to a pale granular mass devoid of processes. This alteration is usually seen only in old inflammatory foci, being rare in acute inflammation. Friedmann also noted in some cells a peripheral chromatolysis.

As a result of these studies, and of other previous investigations, Friedmann was convinced that the above forms of change, partially corresponding to Meynert's "simple atrophy" and "cloudy swelling," indicate a distinct pathological condition in the ganglion cell. He was unable to find them in normal specimens or as the result of physiological involution processes (pigment degeneration). He concluded also that a partially degenerated cell may still functionate.

III.—*Landry's Paralysis.*—In Landry's paralysis degenerative changes in the ganglion cell have been described by Ottinger and Marinesco,[102] Ballet,[103] Remlinger,[104] Bailey and Ewing,[105] Marie and Marinesco,[106] Piccinino,[107] and Mills and Spiller.[108] These lesions consisted in all stages of chromatolysis, peripheral, perinuclear, and general; in the molecular disintegration of the achromatic substance, with the formation of vacuoles and clefts; irregularities in cell outline, and rupture of processes (Marinesco); and in a series of nuclear changes, terminating in the loss of this structure. These lesions have been found in cases showing distinct exudative inflammatory changes, both in the vicinity of and at a distance from the inflammatory foci. *In the case of Piccinino, they were of general distribution, but distinct evidences of exudative inflammation were absent, although numerous cocci were found in the vessels and tissues.* This case seems to furnish a much needed transition stage between fatal cases of Landry's paralysis, without lesions demonstrable by older methods, and the well marked forms with myelitis, and would apparently confirm the belief expressed by Bailey and the writer, that the employment of Nissl's stain would serve to explain this enigmatical group of cases, in which no lesions have hitherto been discovered.

IV.—*Tabes.*—It was anticipated that the employment of Nissl's stain in the study of tabes would greatly enlarge the knowledge of the early pathological changes in this disease, if not certainly determine the seat of the primary lesion.

The researches of Wollenberg, Strobe (see Schaffer),[109] and others, who by the application of Weigert's and Van Gieson's staining methods, had demonstrated a considerable variety of lesions in the spinal ganglion cells in tabes, indicated that the primary lesion is located in these ganglia, and that more delicate technical methods might reveal some earlier lesions not previously demonstrated.

Schaffer[110] examined the cord of a fatal case of tabes, with Argyl-Robertson pupil, Westphal's symptom, and joint lesions. The cells of the cervical cord were nearly all normal. In the lumbar region there were some normal cells, but many showed a fine subdivision of chromatic bodies and diffuse staining about the nucleus, while in others, this alteration had become general.

Marinesco,[111] in a case of general paresis and tabes, found marked central chromatolysis and eccentricity of nuclei in the cells of Clark's column. He endeavors to explain thereby the loss of reflexes in this disease, suggesting that the loss of centrifugal trophic influences which no longer reach these cells, on account of the impairment of the sensory root fibres, induces the cellular lesions described. Similar changes, which he states have been found in the anterior horn cells of tabes, may account for the relaxation of muscles and ligaments, characterizing tabes.

On the other hand, Babes and Kremnitzer,[112] as a result of their study of a case of tabes, conclude that the lesions in the spinal ganglia demonstrable by Pal's and a

modified Nissl's method, are inadequate as a basis for the clinical symptoms found in tabes.

Schaffer also found no pathological alterations demonstrable by Nissl's method in the cells of the spinal ganglia in three cases of fully established tabes. The cells showing advanced chromatolysis described by Marinesco in the spinal ganglia of tabes he identifies as the clear type of cells normally present, according to Lenhossek, et al., in these ganglia.

Juliusberger and Meyer[113] also report the entire absence of chromatolytic or other changes in the spinal ganglion cells in two cases of advanced tabes. While agreeing with Schaffer that these cells are usually of normal appearance in tabes, they fail to regard this fact as evidence against the belief that the spinal ganglia are the primary seat of the lesion in this disease. According to Juliusberger and Meyer the normal appearance of the spinal ganglia in tabes may indicate only that these cells have adjusted themselves gradually to their new and abnormal environment and still retaining their functions, at least in part, have preserved their chromatic structures.

Finally, the writer found no marked or characteristic cellular lesions in the lumbar cord of a well advanced case of tabes, dying from intercurrent pneumonia, while the chromatic structures in the cells of the adjacent spinal ganglia were remarkably well preserved. In this case, however, the disease had long been stationary.

The weight of evidence as gathered from the above observations, indicates very strongly that neither is the primary lesion in locomotor ataxia to be found in the cells of the spinal ganglia, notwithstanding the arguments of Juliusberger and Meyer, nor are these ganglia affected in

any degree comparable to the changes found in the posterior tracts of the cord.

V.—*Descending Bulbar Paralysis.*—Marinesco[114] reports, in a case of this description, advanced chromatolysis in the cells of the XII, VII, VI, and III, cranial nuclei and in the anterior horn cells of the lower medulla. He hesitates, however, to claim that these changes are characteristic of the disease, as it is not yet known how often they occur in normal cases, nor what is their relation to the states of activity and repose, nor to what extent they may be produced by fever or artificial agencies.

VI.—*Diseases of the Cortex.*—In *dementia paralytica* Nagy[115] found various phases of chromatolysis and cellular degeneration up to complete disintegration of the ganglion cell. These lesions were most general in the frontal lobes and most advanced in cases with epileptiform seizures. In cases of *mania*, he found the earlier stages of chromatolysis.

Berger[116] examined the anterior horn cells in twelve cases of *dementia paralytica*, and found lesions affecting principally the chromatic substance in 83 per cent of these cases. He failed to find a strict parallel between these cellular lesions and those of the fibres and cortex, or between them and the clinical symptoms of dementia and paralysis.

Boedecker and Juliusberger[117] found a marked reduction in the number of cortical cells and various grades of chromatolysis and cellular atrophy in three cases of *paralytic dementia.*

In *general paresis* Belmondo[118] has described advanced lesions in the cells of the *zona Rolandica* and in the frontal lobe, while in other parts of the cortex the cells were moderately chromatophilic. The type of lesion observed

seems to be that of a molecular degeneration, in which chromatolysis is followed by changes in the achromatic substance, with partial atrophy and marked pigmentation.

Crisafulli[119] also notes in the same disease a great variety of cellular changes, most advanced in the frontal lobes, although the lesions were not limited to this region. He found pallor, granular disintegration and loss of chromatic substance. The cell bodies were often atrophic or contained an excess of yellowish pigment, and their numbers were reduced. The nuclei were often eccentric and all stages of the destruction of the nucleus were observed. While the alterations shown by Nissl's method were not less constant than those demonstrable by other methods, Crisafulli does not consider them characteristic of the disease, or in any way different from those seen in some other diseases.

In *epileptic insanity*, Tirelli[120] describes similar lesions in the cortical cells. He believes that the cellular lesions in the cases are not specific, but depend largely upon nutritive disturbances, probably of the nature of deficient oxygenation. On the other hand, he believes that the lesions of Purkinje's cells are related to distinct cerebral processes, and are specially dependent upon convulsive seizures (Cf. the writer's observations on eclampsia).

In *general insanity*, Christiani,[121] also, describes very distinct cortical lesions. The cells in this case showed peripheral and perinuclear chromatolysis, their outlines were indistinct or irregular. The achromatic substance was chromatophilic and gave evidence of granular and pigment degeneration, and the formation of vacuoles. The processes were often pale, atrophic, and varicose. The nuclei were often granular, deformed, and eccentric.

In a case of *progressive paralysis*, Heilbronner[122] de-

scribed the various milder grades of chromatolysis which he had noted in the cortical cells. The lesions resembled those seen in alcoholic neuritis, and after section of nerve trunks.

In an acute case of *paranoia*, Cramer[123] found the large pyramidal cells of the cortex to be homogeneous, and only in a few cells could he find any granular detritus of the chromatic structures.

In *acute delirium*, Alsheimer[124] describes three distinct conditions of the cortex.

First.—All cortical regions are affected. The cortical cells are distinctly swollen, and there is general chromatolysis; the processes are visible for long distances (partial chromatophilia). The nuclei are little altered. Cases of cerebral neurasthenia (erschöpfungspsychosen) showed changes of this character.

Second.—All cortical regions are affected. The cells are swollen, their processes are traceable for long distances, the chromatic structures are fused together in a spongy or faintly reticulated mass. Nuclear changes are present, there being a distinct tendency toward cellular degeneration. The "intoxication psychoses" are associated with changes of this type.

Third.—The deeper cortical layers are chiefly affected. The cells are in an advanced stage of degeneration and are often atrophic. The nuclei are swollen and irregular. Here belong the cases of acute delirium occurring in the course of chronic mental diseases. From his observations, Alsheimer concludes that the term "acute delirium" at present includes a variety of entirely different pathological processes.

In a case of *idiocy* in a girl two and one-half years of age, Warda[125] found that the cells were reduced in number,

their protoplasm granular, their nuclei pale, and often lacking in nucleoli.

The extensive monograph of Hammarberg[126] translated and published by Henschen, shows that the essential lesions of *idiocy* consist in congenital deficiency in number and development of the cortical cells. The more recent lesions in the chromatic substance of these cells are therefore of secondary origin and importance.

Juliusberger[127] examined the anterior horn cells in two cases of *epilepsy* dying from convulsions, and found all stages of chromatolysis in many cells. He regards these lesions as identical with those seen after ligature of the aorta and in poisoning by arsenic.

The review of the above cases indicates that in various mental diseases, the chromatic structures of the cortical cell are found after death to be considerably disturbed. With the possible exception of the studies of Alsheimer, it does not appear that any connection has been established between these cellular lesions and the mental disorder from which the patient suffered. In most of the reports the authors have failed to detail the immediate cause and manner of death, although, of course, such information is required before any conclusions may be drawn in regard to the significance of the cellular lesions found in these cases.

B.—*Acute Intoxications.*

Much of the experimental study of Nissl's method has referred to the pathological changes in ganglion cells, induced by the administration of various mineral or vegetable poisons.

Arsenical Poisoning.—In 1891 Erlicki and Rybalkin,[128] examining the spinal gray matter stained by carmine, from

cases of chronic arsenical poisoning, noted a loss of striation in the cell bodies which was probably referable to the destruction of chromatic masses. By the same method they observed that the number of cells in the anterior horns was reduced, that the borders of the remaining cells were rounded, that the dendrites were often lost, and that many cells were reduced to a mass of yellowish granules.

Nissl[129] first described the lesion of acute and chronic arsenical poisoning in rabbits. He found as the first effects an increase in size, rounding of contour of the chromatic granules, and deeper staining of the achromatic substance. Soon the enlarged bodies began to grow paler, to look "crumbly," and were at last subdivided into many fine granules, so that the entire cell body appeared "dusty." Finally even the fine granules disappeared, and the cell sometimes went on to disintegration. During the early stage of chromatolysis fine granules appear in the achromatic substance indicating a simultaneous change in this element of the cell. These changes begin at one pole and gradually involve the entire cell.

Schaffer[130] in 1893 also employed Nissl's method in the examination of changes in ganglion cells from arsenical poisoning. He administered 149 cc. of $\frac{1}{10}$ per cent. sol. of potassium arsenite to a dog during 65 days, thereby producing paresis of the hind legs. He found that the first effects of the poison were the appearance of light points in the peripheral chromatic bodies, which gradually increase in size until the whole mass is bleached and pale. In a rabbit dying after six days from arsenical poisoning, the bleaching of the chromatic bodies appeared to affect the entire chromatic mass from the first. Finally, the entire cell body showed a number of small, pale, bluish granules, the detritus of the chromatic bodies.

According to Schaffer, the lesions produced by chronic antimonial poisoning are similar to those from arsenic.

The recent studies of Lugaro[131] of the effects of arsenical and lead poisoning support the results of Nissl and Schaffer. Lugaro finds that the chromatic bodies are at first altered as these authors describe. Later the achromatic substance is involved and when this point is reached the lesion is probably permanent. The character of the lesions produced by mineral and other poisons according to Lugaro, varies both with the nature of the poison and the type of cell.

Dexler[132] has recently reported a study of chronic arsenical poisoning and its effects, in the spinal cells of the horse. He discovered relatively few changes in the cord below the cervical region. In the cervical region many normal cells remained. Others showed a circumscribed area devoid of chromatic bodies, while some were entirely bereft of chromatic substance, or beset with fine granules.

In a few cells the chromatic bodies had become homogeneous and the achromatic substance was deeply stained.

Lead Poisoning.—Schaffer's studies were extended also to the effects of chronic lead poisoning in rabbits and dogs. The first change noted was a subdivision of perinuclear chromatic bodies into fine granules, with the appearance of fine vacuoles in the peripheral bodies, and leading finally to the well known "dusty" appearance of the cell. In many cells he further describes the alterations now termed "diffuse chromatophilia" and regarded as artifacts.

Nissl[133] reports that the changes due to lead poisoning in rabbits consist in granular disintegration of the chromatophilic bodies of spinal ganglionic cells, while only the borders of the larger and more resistant masses are bleached. In the cortical cells, while the chromatic

substance is lost, the achromatic portion stains deeply, and the outlines of the cells are intact.

Sarbo[134] and Nissl[133] both find that in subacute *phosphorus poisoning* the anterior horn cells of the rabbit show chromatolysis, beginning irregularly at one or more poles of the cell, later affecting the entire cell. The nucleus becomes homogeneous and darkly stained.

Somewhat indefinite changes are referred by Nissl to the effects of *silver poisoning*, from which the chromatic bodies of the spinal stichochromes gradually fade, while the achromatic subtance stains deeply and is transformed into a dark reticulated structure. This process leads to a characteristic striation by light and dark lines in the axis cylinder process. Later, the cells become atrophic, but chromatic bodies may persist.

Strychnine Poisoning.—Somewhat peculiar changes have been described by Dehio[135] and Nissl, after poisoning by strychnine. After fatal doses, followed by convulsions, Dehio found that the medial dorsal group of spinal stichochromes was most affected, while the cells of the posterior horns and spinal ganglia remained normal. The chromatic bodies of the spinal stichochromes stained very deeply, and were in some instances reduced to a mass of fine granules.

Nissl finds that in subacute strychnine poisoning, the changes are characteristic. The achromatic substance stains diffusely, while the chromatic bodies are thicker, more closely packed together, and appear coarsely granular. Often these bodies are condensed about the nucleus leaving the periphery of the cell homogeneous, but deeply stained, while the dendrites are very distinct.

Maneresi[136] states that strychnine poisoning causes an

increase in the size of the nucleus, while chloroform reduces the volume of the nucleus in the spinal stichochrome.

Cellular lesions of a very similar character but usually less definite, have been described as resulting from the administration in poisonous doses of veratrine and trional by Nissl[133]; of nicotine by Vas[137] and Pandi[138]; of cocaine, antipyrine, and the bromides by Pandi; of morphine by Sarbo and Saratschow[139]; of bichloride of mercury by Dotto[140] and by Tirelli[141], of carbonic oxide and sulphuretted hydrogen by Borro[142]; and of phosphorus by Rossi[143].

Alcoholism.—The effects of alcoholic poisoning in the ganglionic cells have been investigated by several writers.

Vas[137] first described the alterations induced in the ganglion cells by chronic alcoholic poisoning. After the daily injection of moderate amounts of alcohol, during a a period of 6 to 12 weeks, a state of general malnutrition was produced in dogs and rabbits, and in this condition the spinal stichochromes and spinal and sympathetic ganglion cells, in areas of irregular distribution, showed central chromatolysis or the lesions described by Friedmann as "homogeneous swelling." These changes he regarded as the result of the general malnutrition of the animal and not of a specific action of alcohol.

Dehio[144] described the changes in Purkinje's cells after acute fatal poisoning by alcohol, administered to rabbits through the stomach. In very acute cases no definite alterations were observed. When the animals lived 18 to 36 hours, characteristic changes were noted affecting the whole or a small portion of the body. The chromatic network of Purkinje's cells was replaced by many fine granules irregularly arranged, while the achromatic substance stained diffusely light blue. The dendrites were

usually unaffected and many normal cells were found. No definite lesions were found in other parts of the central nervous system.

Andriezen,[145] investigating the lesions of alcoholic insanity by Golgi's and Nissl's methods combined, found by the latter, in the cortical cells, moderate chromatophilia of the cell body, swelling and indistinctness of the chromatic masses, thickening of the intranuclear network, and increased pigmentation.

Berkeley[146] investigated the lesions of alcoholic poisoning in the cortical nerve cells by Golgi's and Nissl's methods combined. Golgi's method revealed a distinct shrinkage of all cortical cells, varicose atrophy of the dendrites, disappearance of the gemmulæ, and a roughening of the cell body. After Nissl's method, the cell bodies stained more deeply than in normal specimens, the chromatic bodies were indistinct, the achromatic substance was moderately chromatophilic, the nuclei contained numerous fine granules, and the nucleoli were much enlarged.

Stewart[147] verified the results of Dehio, injecting alcohol into the peritoneal cavity of cats. Both in Purkinje's cells, and less evidently in the spinal stichochromes, chromatolysis, most marked peripherally, and diffuse staining of the achromatic portion of the cells, were observed.

The writer is unable to contribute anything in the experimental study of alcoholism, but his series of cases furnish two examples of fatal alcoholism in which very striking cellular lesions were found throughout the central nervous system.

These cases were males, aged 25 and 29 years. They

died after prolonged periods of intoxication lasting six and twelve weeks respectively, in the typical condition of *delirium tremens*. The temperature rose before death to 104° and 105°. One case was complicated by acute degeneration of the kidneys, the other by terminal catarrhal pneumonia of slight extent. These cases represent the ordinary conditions found in fatal alcoholism in the human subject, and in spite of the complications, some of which are almost always present in such cases, are believed to represent in considerable purity, the lesions produced by prolonged alcoholic poisoning in the human subject. No such lesions have been found by the writer after fatal nephritis, pneumonia, or as the result of a temperature of 106°.

The autopsies were made six and twelve hours after death, and the preservation of the tissues (Lang's fluid, twenty-four hours) was satisfactory. In both cases the lesions demonstrable by Nissl's method were nearly identical.

In the *spinal, medullary, and cortical stichochromes* the usual type of lesion was that of extreme chromatolysis. No normal cells were seen anywhere, and in only a few were there any traces of the peripheral ring of chromatic bodies, often seen when the disintegrating process begins about the nucleus.

In many cells, especially in the cranial nuclei, the lesions had advanced far beyond simple chromatolysis, and the cell outlines were irregular and ragged and considerable areas of the cells were almost transparent. The remains of the chromatic bodies appeared as a uniform deposit of fine granules or in the form of a network of fine granules, or no traces of them could be found. In badly altered cells, the nuclei were almost invariably markedly eccentric

or projected beyond the cell border. They were not found to stain diffusely. Yellowish granular pigment was rarely seen in these cells.

Many of the *Purkinje cells* contained a moderate number of large distinct chromatic bodies, but usually these bodies were thin, ragged, granular, or absent, the deficiency being most marked at the poles and not about the nuclei.

In the *cortical archyochromes* the chromatic network was markedly bleached, sometimes coarsely granular and indistinct.

All through the central nervous system, the dilatation of capillaries was striking. In the first case (the patient was said not to have been sober for three months) the chromatolysis was usually more complete than in the second.

It appears, therefore, that acute alcoholism in the human subject is associated with lesions in the ganglion cells, comparable with, but much more marked than those found after experimental alcoholic poisoning in animals, nor can one hesitate to attribute in large measure the violent nervous symptoms observed in these cases, to the cellular lesions revealed by Nissl's stain and only faintly indicated by other technical methods.

Carbolic Acid Poisoning.—Two cases of fatal poisoning by carbolic acid have come into the writer's hands for examination by Nissl's method. The ages of these subjects were twenty-two and forty years. Each had swallowed a large quantity of the acid with suicidal intent, and both died within two or three hours, with the usual well marked symptoms. At the autopsies made twelve and twenty-four hours after death, the gastric mucosa was found deeply necrotic. The brain and cord after removal exhaled a strong odor of carbolic acid, and it was evident that the poisonous agent had reached the

central nervous system in considerable concentration. The cellular lesions found in these cases were indistinct, and unsatisfactory, a result for which the early deaths may be held responsible.

In the *cortical archyochromes* the meshes of the chromatic network were often much widened. The distinctness of the network was unchanged. In the *spinal* and *cortical stichochromes*, the only changes discovered was an irregularity and raggedness of the chromatic bodies. Many of the large stichochromes appeared normal in every respect. About some of these large cells there was a peculiar diffusion of homogeneous chromatic substance, outside the cell, which the writer is forced to regard as artificial, although it was not found in any other conditions. In both cases a few examples of partial perinuclear and peripheral chromatolysis were noted among Purkinje's cells and the cortical and spinal stichochromes.

The examination of these cases failed to show any characteristic lesions as the result of fatal poisoning by an agent inducing pronounced nervous symptoms, such as coma, convulsions, and paralysis, and indicates that the functions of ganglionic cells may be very largely inhibited, perhaps completely, without leaving morphological changes demonstrable by Nissl's method.

That cases of longer duration will furnish distinct general cellular lesions seems very probable.

Hydrochloric Acid Poisoning.—A case of poisoning by hydrochloric acid came under observation during the course of this study.

Male, 48 years. The patient was said by friends to have swallowed the contents of a bottle labeled "muriatic acid." He was seized with violent pain in the epigastrium and brought in an incoherent mental condition to the hospital, dying twelve hours later with symptoms of shock.

Autopsy three and one-half hours after death. There was superficial necrosis of the lips, mouth, œsophagus and stomach. The stomach and small intestine was filled with a bloody fluid of strongly acid reaction. The blood was everywhere fluid and of a brilliant red color. The lungs were very œdematous. The viscera, especially the liver and kidneys, were intensely congested.

Fixation, 97 per cent alcohol. In the *cord* and *medulla* a great variety of the earlier stages of chromatolysis were observed. The main features of the lesion in these cells were the subdivision often minute, of the chromatic bodies, which gave the cells a rather diffusely stained appearance, and irregularity in the outlines of many cells. All cells appeared more or less affected. Central chromatolysis was rare. In the *cortex* the changes were rather more distinct than elsewhere. The large *ganglionic cells of the motor areas* showed extreme subdivision and irregularity of chromatic bodies. The chromatic network of the *archyochromes* was granular and very irregular. No distinct nuclear changes were observed.

Purkinje's cells showed an extreme reduction in the size and number of the chromatic bodies. There was distinct chromatophilia of the achromatic portion of the cell, not affecting the nuclei, which appeared very clear. With the exception of the tendency toward diffuse staining, none of these features can be regarded as specific, while the chromatophilia, if not accidental, is probably to be referred to a slightly altered reaction of the nervous tissue and cannot be regarded as indicating a vital process.

There was one small hemorrhage in the floor of the fourth ventricle at the level of the sixth nucleus.

Morphine Poisoning.—The present series includes three cases of poisoning by morphine.

Case I.—Male, 45 years. Had been addicted to the use of the drug for several years, finally using 16 grains of morphine hypodermically injected, each day, and had suffered in an extreme degree from the general symptoms referable to this habit. Was said to have eaten nothing for one week before death. After a very large injection, quantity unknown, was brought to hospital in coma, dying within a few hours with typical symptoms of morphine poisoning.

Autopsy six hours after death. There was moderate fatty degeneration of heart-muscle, liver, and kidney. The lungs were very œdematous, and the viscera showed

marked venous congestion. The pancreas was very atrophic, being largely replaced by fat. There was considerable œdema of the brain.

Fixation, Lang's fluid, 24 hours.

The chief feature of the changes revealed by Nissl's stain was a marked diminution in the quantity of chromatic substance in nearly all cells of the central nervous system. The chromatic bodies in the cells of the *cord*, *medulla*, *cerebrum*, and *cerebellum*, were very deficient in size and number or often entirely absent. *Purkinje's cells* were very faint, showing a few small, narrow chromatic bodies, very regularly arranged in concentric rings. Nuclear changes, as a rule, were not noted.

In the *medullary nuclei*, there were some cells still retaining chromatic bodies of considerable size but markedly subdivided. In some of these cells the nuclei were shrunken and often eccentric.

The quantity of yellowish granular pigment was much more abundant than usual in most regions of the central nervous system.

Case II.—Female, age 24 years. Had been addicted to the moderate use of the drug for a few months only, but was able to attend regularly to her work as dressmaker. In a fit of despondency she took a large quantity of morphine by mouth, and in spite of treatment, died twelve hours later, with typical symptoms of morphine poisoning.

Autopsy six hours after death.

There was extreme œdema of the lungs, and marked venous congestion of all viscera, but no other gross lesions of importance.

Microscopical examination. Van Gehuchten's fluid.

The *stichochrome cells* throughout the central nervous system showed changes which in many respects were peculiar. When examined with a low power these cells appeared to have lost their normal distinctly striated appearance, many appearing diffusely and unevenly stained, while their outlines were extremely irregular. When examined with a high power, the above peculiarities were found to consist in a marked subdivision of the chromatic bodies, which were enlarged and very irregularly and minutely subdivided.

In the *medulla* the large cells were extensively altered, further, by the appearance of *clefts* in the cell bodies, similar to those described in other conditions by Nageotti and Etlinger.[148] In this region also the loss of chromatic substance was very uneven, some areas of the cells appear-

ing completely bleached, others showing the minute subdivision, while in some spots the chromatic masses seemed fused together.

The majority of the cell nuclei were shrunken and markedly eccentric, while the loss of chromatic substance was as a rule greatest about the nucleus. About many of the nuclei irregular masses and rods of chromatic substance were heaped. See Plate VI, Fig. 5.

Throughout the cortex changes of a similar character were noted. *Purkinje's cells* of the cerebellum were less affected than the cells of most other regions.

The irregularity in the effects of the chromatolytic process, the ragged appearance of the cell borders, the appearance of clefts, and the frequency of central chromatolysis associated with eccentricity of nuclei, are the features peculiar to this case. The last mentioned abnormality is of special interest in connection with the well-known effect of morphine upon the peripheral nerve filaments.

Case III was identical in all important respects with Case II.

Miscellaneous Intoxications.

Effects of Snake Poison—Phisalix, Charrin and Claude[149] report the examination of the nervous system by Nissl's method in a rabbit dying some time after a series of injections with the poison of the viper. Five injections were given in a period of two weeks and the animal fell into a state of cachexia, marked by partial paralysis and anæsthesia of the limbs, and died at the end of three months. The nerve trunks showed advanced lesions of parenchymatous neuritis, while the cord presented the changes of myelitis. A great variety of changes were noted in the cells, including total loss of chromatic structure, loss of processes and beginning atrophic lesions.

Effects of Poisoning by Blood Serum.—Uhlenhuth and Moxter[150] killed rabbits by two to ten daily injections of the serum of beef and human blood, and found uniformly

in the spinal stichochromes the milder grades of peripheral chromatolysis, and swelling of the remaining chromatic bodies. Many of the animals died in convulsions.

Effects of Toxines of Bacillus Botulinus.—In animals dying with characteristic symptoms of poisoning after the injection of the toxines of the *bacillus botulinus* (isolated from decaying meat by Van Ermengen) Marinesco[151] found very extensive lesions of irregular distribution throughout the central nervous system, most marked in the medulla, basal ganglia, and cord. The earlier changes consisted in simple granular chromatolysis, peripheral or perinuclear, with swelling of the cell body and dendrites, and without alteration in the achromatic portion or nucleus. Later, lacunæ formed in the cell body from destruction of the achromatic substance, and it appears from the report that certain nuclear changes were usually but not always associated with this affection of the achromatic structures. The lesions resembled those following experimental anæmia.

Kempner and Pollak[152] report some interesting observations on the condition of the nerve cells in experimental poisoning by the toxins of *bacillus botulinus*. The changes described are very similar to those noted by Marinesco.

In animals dying after a full dose of the toxine there was complete dissoluton of the chromatic structures of the anterior horn cells. The first distinct changes were noted only after the lapse of twenty hours. The injection of anti-toxic serum nine hours after the toxine prevented the cellular changes, and if withheld for twenty-four hours, sufficed to save the animal's life, but not to prevent marked cellular lesions. They failed to find a distinct parallel between the severity of the symptoms and the grade of cellular lesions.

C.—*Auto-Intoxications.*

Eclampsia.—The central nervous system was fully examined in two cases of eclampsia, and the cord alone was secured for study in one other.

Case I—Multipara, aged 38 years, was brought into the Sloane Maternity Hospital in convulsions, which had for fourteen hours been recurring in rapid succession. The uterus was promptly emptied, and the patient kept under light anæsthesia by chloroform. She received also rectal enemata of chloral, an intravenous infusion of hot salt sol. and was placed in a hot pack. The urine boiled solid with albumen, and was finally suppressed. The temperature rose to 106.8°. She died about twenty-four hours after the first convulsion.

The autopsy was held one and one-half hours after death, and revealed advanced chronic diffuse nephritis and hemorrhagic hepatitis, without other lesions of importance.

Microscopical examination. Lang's fluid.

The *spinal* and *medullary stichochromes* showed a great variety of appearances resulting from alteration of the chromatic bodies. A few cells appeared nearly intact. Most of them showed a moderate grade of chromatolysis, usually peripheral. Some had lost nearly all trace of chromatic bodies, and were extremely pale. The nuclei were often eccentric.

In *Purkinje's cells* there was a peculiar type of advanced change, consisting in complete or nearly complete loss of chromatic bodies, with a fine granular network persisting. The nuclei were shrunken and moderately chromatophilic. The nucleoli were enormously swollen, and many contained three to six small vacuoles. Plate VI, Fig. 6.

In the *cortex* the small pyramidal cells were very pale, from deficiency of chromatic network, but without distinct nuclear changes. The large and giant pyramidal cells showed marked subdivision and loss of chromatic bodies.

Case II—Multipara (8th child), 35 years; brought to hospital in semi-conscious condition. There was marked general œdema. The urine was scanty and highly albuminous. There was one violent eclamptic seizure before delivery, which was promptly effected, and one afterwards. A hot pack caused slight diaphoresis, but the pulse failed rapidly, the temperature remaining low, and she died six hours after admission.

The autopsy, twelve hours after death, showed slight chronic nephritis, hemorrhagic hepatitis, a deep cervical laceration, running above os internum. Hemorrhage was partially responsible for the death.

Fixation, Lang's fluid.

Microscopical examination. Lang's fluid.

The *spinal* and *medullary stichochromes*, with few exceptions, showed moderate or advanced chromatolysis, either diffuse, peripheral, or perinuclear. In the *nuc. X* most of the cells showed marked central chromatolysis with eccentricity of nuclei. In the *Purkinje cells* there was minute subdivision of the chromatic bodies, but no nuclear changes. The large and small pyramidal cells of the *cortex* showed moderate grades of chromatolysis of various types.

In a third case of eclampsia, dying on the third day from pneumonia, very slight changes were found in the spinal stichochromes. The brain could not be secured.

With the exception of the nuclear changes in the Purkinje cells of the first case, no peculiar cellular lesions were noted in these cases of eclampsia. The condition of Purkinje's cells being only an isolated observation, it will be sufficient to place it on record without drawing any conclusions as to its probable significance.

Uræmia.—The cellular changes in the central nervous system in experimental uræmia of dogs, have been studied by Acquisto and Pusateri.[153] In the anterior horn cells of the cord they found loss of peripheral chromatic bodies, while the perinuclear bodies had undergone granular disintegration. In the cerebral cortex different stages of chromatolysis were noted. In some cells the peripheral chromatic bodies and the dendritic spindles were normal, while in the perinuclear zones there was advanced chromatolysis. Other cells were homogeneous, and their nuclei dark and indistinct.

Sacerdotti and Ottolenghi[154] also examined the central nervous system in dogs dying four to seven days after ligature of both ureters. By Golgi's method they demon-

strated varicose atrophy of the dendrites while the axis cylinder process remained normal. The lesions were most marked in the cerebral cortex where all cells were affected, but were also abundant in the *pes hippocampus*. Nissl's stain failed to show the chromatolytic changes in the cortical cells described by Acquisto and Pusateri. They did not examine the medulla.

Donetti[155] examined by Golgi's and Nissl's methods the central nervous system of rabbits dying from uræmia after bilateral nephrectomy. By Golgi's method he found varicose atrophy of dendrites with other less definite changes in the cortical, cerebellar, and spinal cells. After Nissl's method there were no distinct alterations in the cortical cells. In the medulla and cord the nuclei of the large cells were very often eccentric, the chromatic substance was reduced in amount, the bodies were finely fragmented, and many cells contained vacuoles. He does not believe that these lesions are characteristic of uræmia.

The writer's series includes six cases of uræmia in which marked cellular lesions were found, of irregular character and distribution.

Case I.—Male, 19 years. Had suffered for one year from frequent headache and nausea. Nov. 9, he suddenly became unconscious, recovering shortly, with paralysis of right arm. Headache and nausea continuing, on Nov. 12, there was a general convulsion, followed by drowsiness. At this time the urine was scanty, s.g. 1010, and contained considerable albumen and a few casts. On Nov. 20 the drowsiness had deepened into coma. Temperature 100°. Nov. 21, after a severe convulsion, he died. Temperature 104°.

Autopsy four hours after death. The kidneys showed extreme changes of chronic diffuse nephritis and were very small. There were no other visceral lesions of importance. The brain and pia were œdematous.

Microscopical examination. Sat. bichloride.

In the *medulla* the cells of the *nuc. XII* were very

slightly altered, the chromatic bodies in a few cells being moderately subdivided. Above the *nuc. XII* there were no perfectly normal cells. The perinuclear zones were usually lacking in chromatic bodies and either entirely homogeneous or presenting a few faint granules. Along the peripheries of the cells, or at the poles, a few bodies usually persisted, but were irregularly clumped or subdivided. Some of the deeper cells were entirely bleached. Many *Purkinje's cells* appeared normal; in most of them the chromatic bodies were finely subdivided.

In the *frontal cortex* the cells showed no distinct alterations, the chromatic network being distinct.

In the *motor areas* the large cells exhibited changes similar to but less marked than those in the upper medulla.

The capillaries were everywhere dilated.

Case II.—Male, 60 years. Excessively alcoholic. Acute illness began April 3, when he was found dazed and helpless on the floor of his bedroom. April 4, he was feverish and complained of pain in the chest and cough. April 6, there were two general convulsions, and he was brought to hospital, comatose, pulse very weak, temperature 104°, urine suppressed. April 8, there were three severe convulsions. Stools involuntary. Urine suppressed. April 9, died; temperature 104°.

Autopsy, five hours after death. The posterior two-thirds of right lower lobe were consolidated. Lying over the spinal column was a single, small, irregular shaped kidney, in a very advanced stage of chronic nephritis.

The pia was very œdematous. The basal arteries were sclerosed.

Microscopical examination. Sat. Bichloride.

The lesions of the nerve cells were similar in nearly all respects to those described in Case I. The changes, however, were more uniform and advanced, and pigmentation was everywhere extreme.

Case III.—Female, 50 years. For three months had suffered continuously from headache, vertigo, œdema of legs, and dyspnœa. The urine contained a large amount of albumen and many granular casts. On her last admission to the hospital vomiting and diarrhœa were added to above symptoms, the urine was often very scanty, and the dyspnœa was extreme. During the last weeks, the intermittent uræmic symptoms became pronounced, and there was continuous mild coma, scanty excretion of urine, and subnormal temperature.

Autopsy one hour after death. The heart was much hypertrophied. The lungs moderately congested. The kidneys were enlarged; the capsules adherent, surface irregular, and presenting a few cysts; the markings greatly distorted.

Microscopical examination. Alcohol 95 per cent.

In the *medulla*, the cells of the *nuc. XII* were very slightly altered, most of them appearing quite normal. Above this nucleus there was uniform subdivision of chromatic bodies in nearly all cells. Central chromatolysis and eccentricity of nuclei were frequent. The superficial *nuc. X*, and nearly all the deeper cells at this level were extensively changed, many of them showing very few traces of chromatic bodies, while the cell bodies were often irregular and the nuclei eccentric. Purkinje's cells showed moderate general subdivision and fading of chromatic bodies.

In the *motor cortex* the chromatic bodies were usually subdivided and often markedly deficient in number. The chromatic network in the cortical archyochromes was usually distinct.

Case IV.—Male, 50 years. Moderately alcoholic. For one year had suffered from cough, spasmodic dyspnœa, anæmia, and dropsy. March 28, admitted to hospital in a state of mild chronic uræmia. On March 30, the delirium had passed into stupor, and urine and stools were voided involuntarily. On April 2, stupor deepened and the temperature, previously normal, rose to 103°. April 3d, with ante-mortem temperature of 107°, he died.

Autopsy, 13 hours after death. Both kidneys were enlarged, and showed advanced changes of chronic nephritis. The pelvis of the right kidney and adjacent renal tissue was the seat of an abscess cavity filled with thick, somewhat dessicated pus. There were many foci of pus throughout the right kidney. The posterior portions of both lungs were partially consolidated. The arteries were moderately atheromatous.

Microscopical examination. Sat. bichloride.

In the *cord* the large cells were usually normal in appearance. In some there was commencing subivision of central chromatic bodies.

The *lower medullary nuclei* were also but slightly altered, most of the cells appearing normal.

In the cells of the *X nuc.* and above this point there was considerable subdivision and loss of chromatic bodies in most of the cells. A few cells appeared normal and some

contained only a few fine granules limited to the periphery or poles.

In the *motor cortex*, the large cells had lost most of their distinct chromatic bodies, but usually a few peripheral masses remained and the chromatic network was distinct.

In *Purkinje's cells* there was considerable diminution in the size and number of chromatic bodies.

Case V.—Female, 63 years. One year previously the right breast bad been removed for carcinoma. For four months she had suffered from cough and dyspnœa; for two weeks, from œdema of legs. The urine had been scanty. March 19, admitted to the hospital, with suppression of urine and vomiting. March 20th, she became drowsy and there were marked muscular twitchings but no spasms. March 21st, deeply comatose. March 22d, died, temperature 99°.

Autopsy six hours after death.

Body much emaciated and very anæmic. There was general carcinomatosis. Both ureters had been lightly compressed by the new growth, causing double hydronephrosis.

Microscopical examination. Sat. bichloride.

In the *cord* and *medulla* many cells appeared quite normal. In the *X cranial nucleus* and above, most of the cells showed a moderate grade of central or diffuse chromatolysis, and in some instances this change was advanced.

In the *Purkinje cells* the chromatic bodies were small and slender, and often deficient in number, especially in the perinuclear zone. There was no distinct powdering of these bodies.

In the *motor cortex* most of the large cells showed advanced subdivision or absence of perinuclear chromatic bodies.

In the archy-stichochromes the meshes of the network were widened and the chromatic bodies finely subdivided. In the *frontal and occipital archyochromes* the meshes of the chromatic network were widened and irregular.

Case VI.—Male, 53 years. Brought to hospital Nov. 10, 1896, delirious, temperature 104°, urine scanty and highly albuminous. Th etemperature gradually fell to 100°, but the delirium, alternating with coma, continued. The urine was finally suppressed. Stools were passed involuntarily. After two days of complete coma the patient died March 24th, temperature 101.°

Autopsy ten hours after death. The posterior portions of both lungs were irregularly and incompletely consolidated. Both kidneys were enlarged and showed the changes of advanced chronic nephritis. In the pelvis of one was a large calculus. The pia was very œdematous, and opaque. The vessels at the base were normal.

Microscopical examination. Lang's fluid.

In the *cord* and *medulla* a few of the large cells appeared normal. Most of them exhibited a moderately advanced stage of central or peripheral chromatolysis, but there were nearly always some remnants of the bodies in all parts of the cell, none being markedly bleached. In the *motor cortex*, the giant cells contained the normal number of chromatic bodies, usually much subdivided in the perinuclear regions.

In the *cortical archy-stichochromes* the chromatic bodies were indistinct and limited to the poles of the cell, the perinuclear zones being partially bleached or occupied by pigment.

In the *Purkinje cells* the changes were of the usual type in uræmia, the chromatic bodies being irregularly deficient in size, form, and number.

General Observations on Cellular Lesions in Uræmia.

The study of the above cases indicates that uræmia, as it occurs in the human subject, is associated with rather marked changes in the chromatic substance of the nerve cells, but these changes are very irregular in character and distribution. As a rule the spinal cells are but little changed in uncomplicated cases. The lesions are most marked in the *medullary nuclei*, especially in the *nuc. X* and above, as well as in the deeper cells throughout the medulla. Here, nearly every variety of chromatolysis may be observed, excepting very advanced or complete bleaching of the cells, which is rare.

The cortical cells are usually better preserved than might be expected from the very marked cerebral symptoms of fatal and prolonged uræmia. In the case dying with severe convulsions (Case II) the cortical as well as the medullary lesions were most marked.

The condition of Purkinje's cells was very uniform in the cases examined, the chromatic bodies of these cells being very irregular in size and shape, and considerably deficient in number.

The effects of pial œdema could not be distinctly traced in the cortical cells.

No distinct or uniform nuclear changes were detected in these cases, although the nuclei were often abnormal in appearance. The achromatic substance of the cortical archyochromes frequently appeared greenish and opaque, suggesting an early stage of pigment degeneration.

In two cases showing a terminal febrile movement reaching 105° and 108°, the cellular lesions did not differ from those seen in cases with subnormal temperatures, and in these cases no changes were found resembling those seen in sunstroke.

The most advanced cellular alterations of the series were seen in the *nuc. X* and deeper cells (nuc. ambiguus) in the case in which severe dyspnœa had been the chief complaint for five days before death.

In general, it seems reasonable to conclude that the lesions of the nerve cells in uræmia are largely referable to local influences and partly also to general toxæmia. Among such local influences may be suggested (1) altered conditions in the peripheral fibres of the cells; (2) local circulatory disturbances; (3) overaction of particular groups of nerve cells; (4) and possibly also the effects of pyrexia.

Finally, in the above cases, there was a fair parallelism between the grade of cellular change and the general severity of the symptoms.

Sunstroke.—The first studies of nerve cell changes in sunstroke as seen by Nissl's method, were reported by Van Gieson (Lambert[15,6]).

In three cases these authors found throughout the central nervous system, extensive changes in the chromatic structures of the nerve cells. As described by Van Gieson, "The placques in some cells were changed in shape and fewer in number. In others they appeared to be broken into fine dust, and again in others have entirely disappeared. The nucleus stained more deeply than normal, and within the nuclear membrane were some minute spherical granules."

These changes Van Gieson regarded as evidences of an acute parenchymatous degeneration of the neuron, resulting from the action of an autogenous poison which he regards as the basis of the symptoms in sunstroke. (See also Van Gieson[157]).

The present series includes three cases of sunstroke in which the nervous system was examined by Nissl's method.

Case I.—Male, 43 years. Excessively alcoholic, and drinking hard for the few days preceding his seizure. He fell in the street August 7th, 1896, and was brought to the hospital in an unconscious condition. Stools and urine were passed involuntarily. The temperature registered 109°. Treatment by ice pack and stimulation. On the following day he was fairly rational, and highest temperature was 104°. On August 9th he again became delirious and died with temperature of 107°.

Autopsy, fifteen hours after death, showed congestion and œdema of lungs and fatty degeneration of the heart-muscle and liver.

Microscopical examination. Lang's fluid.

In the cervical and lumbar *cord* the large cells stained rather faintly, the chromatic bodies being present, of nearly normal size and shape, but staining faintly. In some cells there was moderate subdivision of chromatic bodies. The nucleoli were nearly all greatly swollen and vacuolated.

In the *medulla*, the same appearances were noted in the larger stichochromes of the cranial nuclei, but in addition the majority of the cells, especially the smaller stichochromes and others, were entirely devoid of chromatic

bodies. The nuclei of these cells contained many chromatic particles, but the nucleoli were not swollen.

In *Purkinje's cells*, very faint outlines of the pale chromatic bodies could with difficulty be distinguished, all of these cells appearing homogeneous by low magnification.

The *cortical cells* were usually quite homogeneous, no traces of chromatic structure being discernible.

In the *posterior spinal ganglia*, the cells were very pale, but here again, the faint outlines of chromatic bodies, often minutely subdivided, could usually be detected. The nucleoli appeared swollen.

In the brain and medulla, less markedly in the cord, all other cells, as well as the ganglia cells, stained very faintly, suggesting that there had been some uniform alteration in the reaction of the tissue which reduced the affinity of all structural elements for methylene blue. No distinct traces of undoubted cadaveric alteration were noted.

The condition of the nerve cells as well as the clinical record, suggest also that alcoholism was quite as important an element in this case as was the thermic fever.

Case II.—Male, 45 years. Found unconscious in the street. Had an empty whiskey flask in his pocket. Brought to hospital comatose, cyanotic, pupils dilated, breathing stertorous, involuntary stools, pulse very feeble, temperature 110°. Died in ice pack fifteen minutes after admission.

Autopsy, eighteen hours after death, showed only fluidity of blood, and intense congestion of viscera. Signs of decomposition were marked in the viscera, but the brain and cord were quite firm.

Microscopical examination. Sat. aq. bichloride.

In the *cord*, the anterior horn cells presented characteristic changes. On low magnification, they failed to show the striated appearance, staining diffusely pale blue. The nucleoli were enormously swollen and pale, and were surrounded by six to ten large deeply staining granules.

With high magnification, it could be seen that some cells still retained traces of chromatic bodies either of the original size and form, or swollen and fused together, or evenly and minutely subdivided, but invariably very pale. These differences may, perhaps, be referred to the varying thickness of the cell body found in the sections. Many cells appeared entirely devoid of chromatic structures. The nuclear membrane was often invisible. The changes

in the majority of these cells were indistinguishable from those found by the writer in over-heated rabbits.

In the *medulla*, nearly all cells showed the more advanced changes noted in the cord. Here many cells were entirely colorless. Some of the *Purkinje cells* were but slightly altered; many contained only a few slender and very pale chromatic masses; some appeared to be devoid of chromatic bodies.

Most of the *cortical cells* failed to show distinct chromatic bodies or network, and the usual nuclear changes were very prominent. In the posterior *spinal ganglia*, most of the cells showed chromatic bodies very pale and minutely subdivided, while many were absolutely colorless. The nucleoli of these cells were much swollen.

In most regions examined, cadaveric changes were noted in the presence of moderate vacuolation and nuclear chromatophilia.

Case III.—Male, 38 years. Alcoholism not certainly known. Treated at another hospital one week before for sunstroke, where he was in a precarious condition, but recovered. On the day of admission fell off a wagon unconscious, and was brought to hospital with usual symptoms. Temperature 109.6°. With treatment in repeated ice packs, he continued twenty-four hours in a half conscious condition, temperature ranging between 97.4° and 105°, but finally died.

Autopsy, three hours after death, showed fluidity of blood, venous congestion of viscera, œdema of lungs, and moderate fatty degeneration of the liver.

Microscopical examination. Sat. bichloride.

In the *cord* the majority of the cells showed a very slight grade of subdivision of the chromatic bodies without any other abnormality. A few cells showed the more advanced changes, with uniform subdivision of chromatophilic bodies, but the loss of chromatic substance was not marked and no very pale cells were seen.

In some of the *medullary nuclei* the pallor and subdivision of the chromatic bodies had reached a considerable degree, and many cells perfectly resembled those seen in Case II, but, on the other hand, the cells in some nuclei showed very little change. In this region, central chromatolysis and eccentricity of nuclei was very frequent in some foci.

In the *cortical cells* the changes in the chromatic structures were not marked, nor in any degree characteristic.

Purkinje's cells, on the other hand, were rather extensively altered, the chromatic bodies being usually finely subdivided, giving the cell a diffusely stained difference.

This case is of special interest as showing that extreme and characteristic lesions in the nerve cells are not always present in sunstroke, and that high temperature alone is inadequate to cause the cellular lesions associated with thermic fever.

The last case was the only one of the three which was comparatively free from the alcoholic element, and the suspicion may well be raised that the marked bleaching of the cells in thermic fever may be partly referable to the complicating alcoholism which is a nearly constant contributing cause in sunstroke.

From extensive studies of the ganglion cells of rabbits, as affected by high temperature, the writer is convinced that the nerve cell changes in sunstroke are specific of this condition, and, in characteristic cases, are distinguishable from most other types of cellular lesions.

Leukemia.

Case I.—Male, colored, 50 years. For past three months had suffered from dyspnœa, general weakness, occasional epistaxis, and pains in the joints. On admission, Dec. 17th, the above symptoms were present, the right knee was swollen and tender, the temperature was 100.° Physical examination negative. Dec. 19th, temperature 103.8°; Jan. 4th there was a mild chill, followed by abdominal pain, tympanites, and temperature 105°. Jan. 8th the blood was examined and 55,000 leucocytes per c.mm., mostly myelocytes, were found. Hemorrhages had occurred from mouth, nose, gums, and bowels. Jan. 9th another chill, temperature 105.4°. Patient in stupor. Jan. 10th, coma, involuntary stools, temperature 104°, death.

Autopsy eight hours after death. The viscera were markedly emphysematous and decomposed, from growth

of *bacillus ærogenes capsulatus*. The abdominal and thoracic lymph nodes were moderately enlarged and very hyperæmic. The spleen was very soft, moderately enlarged, pulp diffluent. The shafts of the long bones as well as all flat bones contained grayish cellular marrow. There were leukemic deposits in the liver, kidneys, and lungs. The brain and cord had escaped marked post-mortem changes and were firm and very anæmic. The pia was œdematous and contained a few small hemorrhages.

Microscopical examination. Lang's fluid.

There was a moderate grade of chromatolysis of very uniform degree throughout the central nervous system. Very few intact cells were found. In the cord, medulla, cerebellum and motor cortex, the chromatic bodies, especially those in the periphery of the cells, were moderately subdivided. The nuclei were usually central and showed no distinct alterations. A prominent feature was the extreme grade of pigment degeneration which affected the nerve cells throughout all parts of the central nervous system.

Case II.—Female, eight years. Had been under observation for four years, suffering from a mixed form of leukemia. During the last few months of the disease, there were extreme anæmia, frequent hemorrhages, extreme enlargement of the spleen. Before death the red cells numbered 880,000, the leucocytes 820,000, consisting of nearly equal numbers of lymphocytes, myelocytes, and polynuclear leucocytes. The patient was confined to bed and quite helpless for three months before death, and during this time there was a moderate febrile movement.

Autopsy six hours after death. The brain could not be secured. The cells of the lumbar cord showed only a moderate grade of central chromatolysis, without special features. The small vessels of the cord were often choked with large mononuclear cells and there were a few larger collections of these cells in the pia.

General Burns.—The present series includes one case of general burns, which proved rapidly fatal.

Female, 40 years. Clothing caught fire from a stove and the skin over three-fourths of the body was severely burned. On admission there was vesication over most of the burned areas, and the patient, though conscious, was in extreme shock. Death ten hours after the accident. The temperature gradually rose, reaching 106.8°.

Autopsy fourteen hours after death. The blood was everywhere fluid, and all the viscera were deeply congested. The brain and cord appeared normal.

Microscopical examination. Ten per cent formalin.

In the lumbar and dorsal *cord* the chromatic bodies were beginning to break up into fine granules and their outlines were very irregular and indistinct. The nuclei appeared normal. The change was most marked about the nucleus. Some cells were apparently unaltered.

In the *spinal ganglia* (lumbar region) there were no cells which retained well-formed chromatic bodies in concentric arrangement. The majority of cells showed only a few scattered chromatic granules and many were entirely bleached. Nuclear changes were absent.

In the *medulla*, the cells were rich in chromatic substance, but the chromatic bodies and network were usually indistinct in outline and partly subdivided. The larger cells of the *nuc. ambiguus* were similar in appearance to those of the cord.

In the higher medullary nuclei, the changes were slightly more advanced, nearly all cells presenting a diminished number of chromatic bodies often partly subdivided.

In the *cortex*, the cells were distinctly paler than normal, from uniform deficiency of chromatic substance. The *giant motor stichochromes* showed marked subdivision and loss of chromatic bodies. Many large pyramidal cells contained no chromatic bodies, but only a faint chromatic network. In *Purkinje's cells*, the size, number, and distinctness of the chromatic bodies were uniformly diminished.

Starvation.—Schaffer[158] described minutely the stages of chromatolysis noted in the anterior horn cells in starving rabbits. Vacuolation was a very marked lesion in these cases, and moderate or extreme nuclear chromatophilia was noted in many cells. Referring these changes directly to malnutrition of the cell, the author concludes that the chromatic substance of the nerve cell represents potential energy.

Tauczek[159] also killed rabbits by complete withdrawal of food and found lesions in the ganglion cells of the cord. After slow starvation he noted disintegration of the chromatic bodies, especially in the spinal stichochromes of the

cervical region. He doubts the propriety however, of referring all changes found under these circumstances to malnutrition of the cells or to any one pathological process.

For the purpose of studying the condition of the nerve cells in states of hunger and complete muscular inactivity, Jacobsohn [160] selected eagles which had been confined in a cold compartment for six weeks, and rabbits killed after being starved for 7 to 10 days. The anterior horn cells of these animals differed in no respect from the normal.

Lugaro and Chiozzi[161] in a study of the cellular changes in the nervous system resulting from prolonged starvation, observed marked degenerative lesions in the cells of the cortex, medulla, cord, and spinal ganglia. These consisted principally in peripheral, central, or circumscribed chromatolysis, vacuolation and disintegration of the achromatic portion of the cell body, and in occasional chromatophilia of nucleus. They used Delafield's hematoxylin to demonstrate the chromatic structures, and noted in the altered cells the distinct reticulated structure of the achromatic substance, where the chromatic bodies had disappeared. The lesions were very irregular in distribution, and not always uniform in degree, while their similarity to the changes observed after poisoning by arsenic or lead was very striking.

The authors conclude that the lesions observed must result from some form of auto-intoxication from intestinal absorption or internal metabolism, which they assume to exist in starving animals.

Donetti[162] has described the lesions in the central nervous system after removal of the suprarenal glands. Guinea pigs survived the operation only 48 hours; rabbits, from 8 to 15 days. The cellular lesions were most marked in the

medulla, but were very irregular in distribution, normal cells lying side by side with extensively altered ones. Some cells seem to be shrunken, others swollen. The nuclei were either central or eccentric. The chromatic masses in the medullary cells were usually reduced to granules and often limited to the poles of the cell. A few cells had lost their nuclei and were in the process of complete degeneration.

Meningitis, Apoplexy and Disturbances of Cerebral Circulation.

Excepting the reference of Marinesco[163] to two cases of pneumonia complicated with meningitis, in which he found the spinal stichochromes but little affected, the writer has found in the literature no reports of studies of the ganglion cells in cases of meningitis.

Dotto and Pusateri,[185] alone, report studies on the cortical nerve cells in cases of intracerebral focal hemorrhages. They found various grades of chromatolysis in the cortical areas whose function had been destroyed by basal hemorrhage. From lesions found in the *Island of Reil* they are led to conclude that this region is connected by fibres running through the external capsule.

The present series includes the following cases of meningitis.

Case I—*Tuberculous Meningitis.*—Male, 29 years of age; suffered from general pains and malaise for one month, headache, nausea, and vomiting, for two weeks, and had been delirious for two days before admission to hospital, Sept. 17, 1896, when he presented distinct symptoms of meningitis, the head being markedly retracted, the limbs rigid and twitching, and the temperature 103°. Delirium alternated with coma, and the temperature remained constant until Sept. 22d, when he died with a temperature of 104°.

Autopsy 13 hours after death.

There was marked œdema of the pia, which was lightly coated with fibrin and pus at the base. The ventricles were considerably distended with turbid fluid. In all these regions and over the cervical cord there were many fine miliary tubercles in the pia. The brain was moderately soft.

There was a small tuberculous focus at the apex of the left lung, and the liver and kidneys showed slight fatty changes.

Microscopical examination. Lang's fluid.

In the *cord* most of the large cells contained the usual number of chromatic bodies, but these were usually very ragged and often finely subdivided.

In the *medulla* the lesions were very irregular in distribution. Most of the superficial nuclei contained cells with many chromatic bodies either well formed or partly disintegrated. Similar cells were seen in the deeper zones, but here the majority of cells were markedly bleached, and presented only a few pale bodies along the periphery. A few of these deeper cells appeared entirely bleached.

It was noted that the cells of one nucleus immediately adjacent to a miliary tubercle showed comparatively little change, while the deeper cells lying more remote from the tubercle were extensively altered. Moreover in some foci entirely bleached cells lay next to very slightly altered ones. Plate VI, Figs. 2 and 3.

In the *motor cortex* the giant cells usually showed marked central chromatolysis, a few were entirely lacking in chromatic bodies, while a few others appeared very little affected. In the *arkyochromes* the network was usually paler than normal. *Purkinje's cells* contained an abundance of chromatic bodies, which were usually reduced in size, irregular in shape and often partly subdivided.

Case II.—*Tuberculous Meningitis.*—Male, 30 years of age. Formerly alcoholic. Illness began January 1, 1897, with symptoms of pulmonary tuberculosis of subacute character. Admitted February 22d, with signs of severe general bronchitis, without pneumonia or cavities, temperature 104°. Urine, 5 per cent of albumen.

On February 23d, he was mildly delirious and passed considerable blood from rectum. Maximum temperature, 103°. On the 27th there was vomiting, diarrhœa, great restlessness, mild delirium, temperature uniform. These symptoms continued until March 1st, when he became comatose, and on March 2d, died, temperature 108°.

Autopsy eight hours after death. The pia over the convexity was dry and granular, at the base œdematous. The ventricles were slightly distended with turbid fluid. The brain was distinctly softened. There were everywhere many fine miliary tubercles. The cervical cord was involved.

The lungs showed the lesions of subacute miliary tuberculosis of moderate extent.

Microscopical examination. Sat. bichloride.

The description of the previous case applies accurately to the present one, with some minor differences. In the second case the tuberculous process was much more active, following the vessels for some distance into the tissues. The marked bleaching of many large cortical and medullary cells described in the first case was seldom seen in the second. It may be noted that coma and rigidity were distinct and prolonged and the distension of the ventricles greater in the first case. In the second, the temperature was much higher and the general toxæmia more intense, but the cellular lesions were less advanced.

Case III.—*Sporadic Meningitis.*—Female, 18 years. Illness began June 28th, 1896, with vomiting and convulsions, passing into coma, which continued till death. On July 1st, the day of admission, there were several convulsions; maximum temperature, 104°. July 4th, several convulsions; temperature, 104.5°. July 6th, the coma deepened; temperature, 102°. July 7th, the breathing became rapid and stertorous; temperature, 105°. July 8th, there was complete coma and the patient died with ante-mortem temperature 105°.

Autopsy seven hours after death. The entire pia and brain were much congested. The pia was everywhere opaque and over the base and along the sulci moderately thickened. The ventricles were not distended nor markedly inflamed. There were no visceral lesions of importance.

Microscopical examination. Lang's fluid.

The pia over the base, convexity, and cervical cord, was much thickened and infiltrated with leucocytes and large mononuclear cells. There were numerous small extravasations of blood. Along the vessels of the brain and medulla there was moderate infiltration with round cells.

The condition of the ganglion cells was similar in most details to that found in the first case of tuberculous meningitis.

CASE IV.—*Chronic Hemorrhagic Pachymeningitis.*—Female, 78 years. Had suffered for six months from headache, gradually increasing hemiparesis with muscular contractures, and from tremor resembling that of paralysis agitans. Two days before death she became unconscious, and died without marked rise of temperature. (The writer is indebted to Doctor Frederick Peterson for the reference to this case).

Autopsy four hours after death. The dura all over the convexity was markedly thickened, lamellated, and infiltrated with blood. In the meshes of pia and arachnoid there was a little free blood widely distributed in a very thin layer over a large area of the convexity. The pia was considerably thickened. The arteries at the base were slightly atheromatous. The cord and viscera could not be secured.

Microscopical examination. Ten per cent formalin.

The preservation and staining were excellent, but thin sections were needed to avoid the appearance of chromatophilia.

The *superficial nuclei of the medulla* were almost entirely normal in appearance, except for excessive pigmentation of the cells.

In the deeper lying cells there was usually an early stage of uniform chromatolysis, the perinuclear bodies being rather finely subdivided.

In the *cortex*, there was also in many cells a slight grade of chromatolysis, but the majority of cells were practically normal. Beneath the thickest portion of the blood clot, the lesions were more general and advanced than elsewhere.

In *Purkinje's cells* there was a moderate reduction in the size and number of the chromatic bodies.

The absence of advanced lesions in this case may reasonably be referred to the lack of serious disturbances in the cerebral circulation. There was very little extravascular blood in the pia, and the resulting increase of intra-cranial pressure must have been comparatively slight.

CASE V.—*Chronic Hemorrhagic Pachymeningitis.*—Male, 37 years. Brought to hospital by ambulance, having had five convulsions. The convulsions continued and he died a few minutes after admission, temperature 101.8°.

Autopsy six hours after death. There was considerable blood in the meshes of a thickened dura over both

sides of the convexity. There was a flat blood clot 10 x 7 cm. and 1 cm. in thickness, lying in the meshes of arachnoid, compressing right parietal lobe. The pia was everywhere moderately thickened. The blood vessels at the base of the brain were normal. The left ventricle was moderately hypertrophied. The lungs showed evidences of chronic congestion. The kidneys were moderately enlarged, capsules not adherent, surface smooth, markings irregular.

Microscopical examination. Lang's fluid.

In the *medulla* the lesions were neither extreme in degree nor very uniform in distribution. Most of the large stichochromes in the lower medulla contained many pale but not disintegrated chromatic bodies. There were, however, isolated examples of advanced chromatolysis. Higher in the medulla and in the deeper lying groups, some moderately bleached cells were observed.

In the *cortex beneath the clot*, the chromatic bodies were limited to the periphery and those present seemed reduced in size. The perinuclear zones were moderately bleached. Many of the large cells, however, showed only a beginning subdivision of perinuclear masses.

Beyond the limits of the clot most of the cells appeared intact.

In *Purkinje's cells* the chromatic bodies were pale, near the dendrites deficient, but elsewhere present in nearly normal number and appearance.

The absence of advanced changes in this case may be referred to the rapidly fatal effects of the hemorrhage. Although no definite history of the beginning of the attack could be obtained, it seemed certain that death followed the initial seizure within two or three hours.

Case VI. — *Chronic Hemorrhagic Pachymeningitis.* — Male, 50 years. For three months had suffered from severe headache and was unable to work. December 1, 1896, he was unable to walk, and was thereafter confined to bed. About January 1st, 1897, he became partially comatose, opening his eyes when roused, but soon relapsing into unconsciousness. January 2d, coma deepened and continued without other noteworthy symptoms, until death, January 12th. The temperature during this period was between 99° and 101°.

Autopsy eight hours after death. The posterior portions of both lungs were partly consolidated from catarrhal pneumonia. The entire convexity of the

brain was evenly compressed by a layer of clotted blood and fibrin derived from a thickened and lamellated dura-mater. This blood clot was 1 to 1.5 cm. in thickness and must have exerted considerable pressure upon the underlying brain tissue.

Microscopical examination. Lang's fluid.

The *cortical cells* from various regions showed a marked deficiency in chromatic substance. In the *motor regions beneath a thick mass of blood*, very few cells showed any distinct traces of chromatic bodies, the majority of cells being extremely bleached, but still retaining a distinct chromatic network. In some cells a few traces of the chromatic bodies persisted in the form of a peripheral ring of small granules. Beyond the limits of the blood clot, these changes were less marked. In the *cerebellum*, which was free from clot, Purkinje's cells contained a considerable number of chromatic bodies moderately reduced in size, and often limited to the perinuclear zone, or the base of the cell.

Case VII.—*Subacute Leptomeningitis.*—Male, 7 years. Had tonsilitis in June, 1896. A few weeks later had a chill, followed by fever, lasting a few days, and had a mild general convulsion. Slight cough and irregular pains continued until September 16th, when he passed a restless night, waking with fever, repeated vomiting, great thirst, and within a few hours had five general convulsions. On admission, the patient was in stupor, temperature 104.8°. September 17th, stupor and delirium, temperature 106°. Urine and stools passed involuntarily. September 18th died, temperature 107.5°.

Autopsy three hours after death. The lungs were congested. The consistence of the liver was reduced and outlines of lobules indistinct. The spleen was moderately enlarged. There was extreme engorgement of all cerebral sinuses and pial vessels. Over the frontal lobes there was a slight effusion of bloody serum along the course of the pial vessels. The ependyma was dry. The pia was congested and opaque, the cortical gray matter darker than normal. No tubercles nor foci of blood or pus were present.

Microscopical examination.

In the *cord and medulla* the large cells showed all stages of destruction of chromatic bodies, many cells in the medulla especially, being entirely bleached. In these bleached cells the underlying reticulum was sometimes

visible, often indistinguishable. Irregularity in outline of cell body, and eccentricity of nucleus were frequently seen. No normal cells could be found.

In the *motor cortex*, the large cells showed all stages of chromatolysis, and many were entirely bleached. The small cells exhibited a pale chromatic network with a few small chromatic granules at one or more poles.

Purkinje's cells were usually extremely bleached, but many still showed faint remnants of chromophilic bodies.

There was everywhere extreme congestion of the blood vessels and marked dilatation of pericellular lymph spaces.

The pia was greatly thickened by a new growth of connective tissue, infiltrated with blood, round cells and leucocytes. A few cocci in short chains were seen in sections.

Case VIII.—*Subacute Traumatic Meningitis and Encephalitis.*—Male, 28 years. January 7th, 1898, was struck on right temporal region by a falling iron door. Was rendered temporarily unconscious, and afterward suffered severe and continuous headache, located in this region. He was often drowsy, but not delirious, and had no spasms or paresis. On admission, February 1st, temperature was 100.2°; pulse, 90; right pupil slightly larger than left; internal strabismus of left eye; some stiffness of neck; spastic rigidity of legs and arms; increased reflexes; no anæsthesia or hyperæsthesia. February 2d, restless, moving hands constantly in incoordinate manner. Temperature 103°. February 3d, mildly delirious, involuntary urine, temperature, 103°. February 4th, stupor, temperature 103.8°. February 5th, internal strabismus more marked. Legs rigid; delirious; temperature 104°. February 6th, temperature 105. February 7th, died, temperature 105°.

Autopsy four hours after death. Over two-thirds of the left convexity, dura, pia, and brain are tightly adherent, and about this area the pia is granular, extremely congested, and ecchymotic. The underlying brain substance is much congested. In left superior occipital fossa, dura and pia are adherent to skull. Both ventricles are moderately dilated with turbid fluid. There are no fractures. Viscera congested.

Miscroscopical examination. Alcohol 95 per cent.

In the *motor cortex* beneath the adherent membranes the chromatic bodies of the giant cells are invariably very

irregular in shape, often much faded and usually much subdivided. In some cells the entire perinuclear zone is replaced by fine granules, and in thick sections appears opaque. The nuclei stain diffusely. In the archysticho-chromes the chromatic bodies are usually limited to the poles and are subdivided. The chromatic network is everywhere retained. On the opposite side of the brain the meningitis is slight, and the same lesions rather less marked are to be observed.

On the under surface of the cerebellum there is a layer of exudate of considerable thickness. Here the *Purkinje cells* are very deficient in chromatic bodies, which when present, are faint, irregular, and subdivided. Many cells show no bodies, but only a distinct but irregular chromatic network.

On the floor of the fourth ventricle in the region of the locus ceruleus and III, IV nuc. there is a rupture of tissue, extending a few lines beneath the surface, and covered with fresh exudate.

The cells of this region are similar to those of the motor cortex, showing marked subdivision of chromatic bodies, while the chromatic network and granular remains of the chromatic bodies are distinctly visible.

In the *lower medulla* the changes are much less marked, many normal cells appearing.

Case IX.—*Intra-ventricular Hemorrhage.*—Male, 30 years. Without previous illness was suddenly seized on March 28th with pain in the head, and was admitted to hospital with right hemiplegia. The paralysis was incomplete and the muscles rigid. Temperature 100°. Urine, passed involuntarily, was highly albuminous. There was deep coma. March 30th, coma persisted, temperature 103°. March 31st, coma and paralysis complete, temperature 107°. Died.

Autopsy four hours after death.

The pia was moderately œdematous, and, over posterior surface of cerebellum, infiltrated with bloody serum. The ventricles were considerably distended with clotted blood and serum. The left optic thalamus, Island of Reil, internal capsule, and temporo-sphenoidal lobe were the seat of a large hemorrhage, 7 to 8 cm. in diameter. The arteries at the base were atheromatous, and there was advanced chronic nephritis.

Microscopical examination. Sat. bichloride.

In the *medulla* the cells of the superficial nuclei show

general and, in the large cells, usually complete chromatolysis. In the cells which are not bleached, there is usually a single mass of chromatic substance at one side or pole.

In the *frontal and motor cortex* chromatolysis is extreme, most of the large cells presenting a wide homogeneous area about the nucleus, in which the cyto-reticulum is with difficulty distinguished.

Some *Purkinje cells* contain the normal number of chromatic bodies, but these are usually very small and slender. Many are entirely bleached. In some the bodies are limited to a narrow peripheral ring.

Case X.—*Extra-dural Hemorrhage.*—Male, 24 years. Fell from a wagon on the evening of March 31st, was rendered unconscious, had one convulsion. Brought to hospital 2 A. M. April 1st, in coma, pupils widely dilated, not reacting to light, breathing slow, stertorous, complete paralysis of limbs. Temperature 105.2°, pulse 64. Died at 4.50 P. M., temperature 109°.

Autopsy ten hours after death.

The entire coronal suture was separated ¼ cm., the fissure crossing the groove of the left middle meningeal artery and passing into left medulla cerebral fossa. The left middle meningeal artery was ruptured. The dura was separated from the skull over an area 14 cm. in diameter by a large firm blood clot. The underlying convolutions were flattened, but not lacerated. The under surface of the left temporo-sphenoidal lobe was extensively lacerated.

Microscopical examination. Sat. bichloride.

The viscera were uniformly congested.

Throughout the *medulla* the deeper cells are extremely deficient in chromatic substance, many being entirely bleached, and the others retaining a very few small irregular masses at one or more poles. The superficial nuclei are slightly less affected.

Throughout the *motor cortex*, more marked on the side of the blood clot, all cells are extensively bleached, the remains of chromatic bodies being scanty, minute and usually limited to the periphery of the cell. In the arkyochromes the network stains faintly. In *Purkinje's cells* the chromatic bodies are uniformly deficient in size, usually also in number, but the lesions are much less advanced than in the motor cortex.

CASE XI.—*Thrombosis of Basilar Artery.*—Male, 35 years. Admitted to hospital for operation on incarcerated inguinal hernia, but on day of admission became comatose and operation was postponed. The coma rapidly deepened and without convulsions or marked elevation of temperature, he died, about 36 hours after the onset of cerebral symptoms.

Autopsy twelve hours after death. There was an incarcerated and partly strangulated right inguinal hernia. The lungs contained a few areas of catarrhal pneumonia. In the kidneys there were a few old infarcted areas. There was moderate general arterio-sclerosis.

At the middle point of the basilar artery there was a firm thrombus entirely occluding the lumen. The brain was moderately œdematous, but there were no areas of softening.

Microscopical examination. Lang's fluid.

Throughout the *medulla* all the large cells are either completely or almost completely lacking in chromatic bodies. In some cells the remains of the chromatic bodies are visible as fine, pale granules scattered irregularly throughout the cell body. In most cells the cyto-reticulum is retained, and there are no evidences of nuclear changes.

In the *cortex* nearly all the large pyramidal cells are very deficient in chromatic substance, but many of them show a few small masses at one or more poles. In the smaller cells the chromatic network is visible but faintly stained.

In *Purkinje's cells* there is a striking diminution in the size and often in the number of chromatic bodies. Many of the cells contain a few pale and very slender rods.

The chief features of this case are the extreme bleaching of the medullary cells and the uniformity in the cellular lesions in this and other regions.

The study of the foregoing cases indicates that purulent and tuberculous meningitis are usually associated with lesions in the chromatic structures of the ganglion cells often of extreme grade, but not of uniform distribution. Immediate proximity to a purulent or tuberculous meningitic process does not necessarily destroy the chromatic

bodies in these cells. On comparison of these cases of meningitis with those of hemorrhagic pachymeningitis in which are added the elements of pressure from extravasated blood or anæmia from thrombosis of vessels, *it will be seen that the character of the lesions changes and that the extreme grades of chromatolysis are, as a rule, uniformly present in the compressed or anæmic areas. Moreover, this fact is the more striking because the effects of bacterial toxine are absent in these latter cases.*

The lesions found in the cases of thrombosis of basilar artery and various forms of cerebral hemorrhage, were equalled in intensity only in cases of alcoholism, sunstroke, tetanus, etc., but not in cases of severe general bacterial toxæmia. The conclusion seems justified therefore that the chromatic substance of nerve cells is more susceptible to the effects of disordered circulation than to the action of most bacterial toxines.

In many of the cases attended with high temperature the lesions were more advanced than in those in which the fever was moderate, but no uniform effect could be traced to this cause.

The severity of the lesions seemed to depend almost entirely upon the extent and duration of the pressure or anæmia (Cf. Cases V and VI).

The relation of cellular changes in the cranial nuclei to the neuritis of cranial nerves commonly present in meningitis, could not be thoroughly studied at this time, but is an interesting subject deserving investigation. "Axonal degeneration" was a common medullary lesion in the cases of meningitis.

In connection with the cases of cerebral hemorrhage it is important to refer to Neumeyer's study[186] of the effects of mechanical pressure upon the cortical cells. Neumeyer

inserted lead plates beneath the skulls of rabbits, diminishing the intracranial capacity about $\frac{1}{20}$. After a few hours of such pressure, the superficial cells showed a progressive loss of chromatic substance both in the nucleus and cytoplasm, the chromatic bodies often being massed into clumps and appearing coarsely granular.

After ten days, only a few granules of chromatic substance remained in the cell body, usually in the perinuclear zone. Often the nuclear membrane seemed to have disappeared. Many cells had lost all trace of cytoplasm, only the shrunken nuclei remaining. These lesions extended about 10 mm. beyond the limits of pressure, gradually fading into normal tissues.

Of similar interest also are the experiments of Pellizzi[187] which indicate that the simple loss of function of the cells in these cases is not sufficient to account for the destruction of the chromatic bodies of the cells. Pellizzi separated the frontal lobe in dogs from most of its fibrillar connections, while leaving the blood vessels partly intact, and found thereafter very minor changes in the chromatic structures of the nerve cells, which remained practically normal for many days. Some of the animals lived as long as two months.

D.—*Infectious Diseases.*

Typhoid Fever.—The writer has been unable to find any complete reports of the examination of the central nervous system by Nissl's method in cases of typhoid fever.

Marinesco,[163] however, states that in two cases of typhoid fever he found very slight cellular changes associated with marked vascular disturbances, such as hyperæmia and hemorrhage.

In typhoid fever and diphtheria Babes[72] refers to the

cellular lesions in the cord as consisting in chromatolysis, vacuolation, and loss of nucleus and nucleolus, associated with vascular changes and increase of round cells.

The present series includes two cases of typhoid fever.

Case I.—Male, 36 years. Had been confined to bed with fever and diarrhœa, and had been delirious four days before coming under observation. On admission, Oct. 22, 1896, the patient was actively delirious, temperature 105, with distinct signs of severe typhoid infection.

Oct. 23, maximum temperature 105.5°. Urine and stools passed involuntarily, pulse very rapid and feeble. Death Oct. 23; terminal temperature 103°.

Autopsy three hours after death. Nearly all the Peyer's patches were the seat of deep necrosis. There were many small ulcers throughout the colon.

The spleen was very large and soft. The mesenteric lymph nodes greatly swollen. No other visceral complications.

Microscopical examination. Lang's fluid, 24 hours.

In the *cord* nearly all the stichochromes showed moderate subdivision of chromatic bodies, most marked about the nucleus. In the *medulla*, the ganglion cells showed all the less advanced types of chromatolysis. In some cells, especially of the *nuc. X* and deeper areas, only a few fine chromatic granules were left. The periphery of the cell was sometimes more affected than the perinuclear area, and in many instances there was a diffuse powdering of all bodies, most advanced near the nucleus. The cells of the *nuc. XII* were little changed, those of the *nuc. X* and *nuc. VIII* and deeper cells above, more markedly.

In the *olives*, the cells showed only a narrow peripheral ring of subdivided bodies.

In the *locus ceruleus* many cells looked normal, others were very deficient in chromatic bodies. The pigment was here of normal appearance.

In the *Purkinje cells* there was uniform diminution in size and often also in numbers of the chromatic bodies, whose arrangement was still regularly concentric.

Case II.—Male, 35 years. Said to be excessively alcoholic. Illness began Dec. 16, 1896, with fever, prostration and diarrhœa. On admission Dec. 20, the patient was mildly delirious, temperature 104, abdomen moderately distended, slight œdema of legs. The delirium and fever

continued unchanged until the 26th, when he became partially comatose, with temperature 105°. On the 28th, the urine and stools were passed involuntarily. With persistent high temperatures, delirium and stupor, on January 2, he died, with slight indications of perforation, and with a terminal temperature of 105°.

Autopsy five hours later. There was a localized purulent peritonitis in right iliac fossa about a perforated ulcer. The lungs contained numerous small areas of catarrhal pneumonia. There were many large and nearly healed ulcers in the location of Peyer's patches, and some more recent ones in the upper colon.

Microscopical examination. Sat. aqueous bichloride. 12 hours; bichloride and formalin 5 per cent; and bichloride and sat. aq. picric acid (aa).

The cord was not examined.

In the *medulla* there was a very marked loss of chromatic bodies, affecting the perinuclear zone or the entire cell body or leaving a few subdivided or irregularly fused chromatic masses at the poles of the cell. The lesion is distinct in the *XII*, *X* and *VIII nuclei*. The deeper cells, including the *nuc. ambiguus* and *nuc. lateralis* showed more pronounced changes, many cells being extremely bleached, often with eccentric nuclei, irregularity of outline, and loss of cyto-reticulum.

In the *cortex* the giant motor stichochromes showed changes similar to those of the medulla. The arkyochromes showed irregularities and partial bleaching of the chromatic network, retaining clumps of chromatic substance at the poles only, and are often ragged in outline. There is distinct pulverization of chromatic bodies in the larger dendrites.

Purkinje's cells were extensively altered, exhibiting many of the more advanced types of chromatolysis. Some of these cells were entirely bleached.

The results of the examination of two cases indicate that in typhoid fever there are cellular lesions of considerable intensity and of general distribution throughout the central nervous system. It would seem that these lesions increase with the duration and severity of the general toxæmia, and are partly influenced by a prolonged high temperature.

They appear also to be essentially connected with the

profound nervous disturbances which accompany fatal typhoid infection.

In the above cases the lesions were much more pronounced than in cases of pneumonia of equal duration.

Pneumonia.—Dejerine[164] in 1897 reported a case of pneumonia, duration three days, with low delirium and a maximum temperature 43.3° C, in which he had examined the spinal stichochromes by Nissl's method. These cells were much altered throughout the cord, being swollen, homogeneous, and presenting only traces of chromatic bodies. The nucleoli stained poorly. Dejerine did not believe that this chromatolysis was accompanied by any marked symptoms, nor could it be considered as a lesion of importance.

Marinesco[163] reports similar results from the examination of two cases of pneumonia complicated with meningitis, and also in broncho-pneumonia.

In the cases complicated with meningitis the anterior horn cells were found unaltered. In cases of broncho-pneumonia, various grades of chromatolysis were noted in the spinal stichochromes. Marinesco seems to refer the result in the latter instance to "the immediate action upon the cells of the more virulent toxine of broncho-pneumonia, while in the first cases the toxines appear to have exhausted themselves in producing the vascular lesions of meningitis."

Marinesco goes on to infer, on grounds not stated, that the lesions of nerve cells in infectious diseases depend upon the age of the individual, being more marked in old persons, upon the intensity of the virus, on the duration of the disease, and as Goldscheider and Flatau[165] have shown, upon the fever.

The present series includes four cases of pneumonia in

which the central nervous system was examined by Nissl's method.

Case I.—Female, 48 years. Two weeks before admission began to suffer from cough with mucoid and blood-stained sputum. Ten days later had a severe chill, complained of pain in the side and was prostrated. On admission was comatose, with paralysis of left limbs, dilated pupils, temperature 106.5°. All symptoms persisted and she died on the 17th day. Temperature 105.5°.

Autopsy 24 hours after death. The upper two-thirds of right upper lobe were consolidated. The pia all over the base and convexity and for some distance down the cord was œdematous and lightly coated with pus, containing large numbers of capsulated diplococci. There was slight chronic nephritis.

Microscopical examination. Lang's fluid, 24 hours.

There was everywhere evidence of post-mortem change consisting in moderate nuclear chromatophilia and vacuolation of the bodies of the ganglion cells.

In the *cervical cord*, which was lightly covered with pus, most of the chromatic bodies were moderately subdivided and irregular, some were but little changed, and a few cells appeared normal.

In the *medullary nuclei* the changes were of the same type but more distinct. The *XII nucleus* was but slightly affected. The *X nucleus* and deeper lying cells were extensively changed.

In the *cortex*, there was a moderate subdivision of chromatic bodies in most of the larger pyramidal cells, but the chromatic network was usually well preserved. Many of the *Purkinje's cells* were extremely deficient in the size and numbers of the chromatic bodies, some appearing almost completely bleached but showing a distinct underlying network. Others were but little changed. Pigmentation was everywhere excessive.

Case II.—Male, 28 years. Brought to hospital delirious, temperature 103°, with consolidation of both lower lobes. Alcoholism suspected. Alternating delirium and stupor continuing for three days, the temperature remained uniformly high, reaching 109° before death, on the fourth day of observation. The urine was moderately reduced in quantity, slightly albuminous and contained coarsely granular casts. All lobes were partly and the posterior portions entirely consolidated. The liver was

slightly fatty. There were signs of moderate chronic nephritis. The pia was very œdematous. The case was a typical example of acute lobar pneumonia in an alcoholic subject.

Microscopical examination. Lang's fluid, 12 hours.

No normal cells were anywhere seen. In the *spinal*, *medullary* and *cortical stichochromes* the usual type of lesion was that of extreme chromatolysis. In only a few cells was the peripheral ring of subdivided chromatic bodies still present. In the *medulla* many cells were entirely bleached, largely infiltrated with pigment and showing extreme eccentricity of nuclei. In many of these cells the underlying reticulum could not be distinguished. *Purkinje's cells* were much less affected than the medullary nuclei. Throughout the medulla there was well marked circumvascular infiltration with round cells of both the pial and deeper vessels. The lesions in this case are probably referable more to alcoholism or high temperature than to the pneumonia.

Case III.—Male, 55 years. Moderately alcoholic. Illness began with severe chills, cough and rusty sputum, and continued for two weeks with the usual symptoms of pneumonia. On admission, at the end of the two weeks, there were signs of consolidation of right upper and lower lobes. The temperature ran between 100° and 102°, till just before death when it rose to 105° F. The patient was emaciated, vomited occasionally, and appeared stupid. The urine was slightly albuminous. Death on the eighteenth day.

Autopsy twelve hours after death. There was consolidation of most of right lung, but no signs of alcoholism or nephritis. The pia was very œdematous.

Microscopical examination. Sat. bichloride, 24 hours.

In the *cord* and *medulla* there was very marked subdivision and loss of chromatic bodies in all the larger cells. The nuclei were often eccentric. Some cells retained small but distinct chromatic bodies. Pigmentation was moderate. Some of the cells closely resembled those seen in the case of alcoholic pneumonia, but none were found entirely bleached.

The *cortical stichochromes* and *Purkinje's cells* showed only moderate subdivision of chromatic bodies.

Case IV.—Female, 40 years. Was seized on July 4th with chills, headache, vomiting and pain in chest, followed

later by cough with bloody expectoration. On admission the temperature was 104° F.; there were signs of consolidation of the right upper lobe and the patient was delirious. The delirium or coma continued, the temperature rose to 106° and remained at that point for five days when with marked abdominal distension and violent delirium the patient died.

Autopsy two hours after death. There was consolidation, with the production of new intraalveolar connective tissue, of the right upper lobe. The pial and dural veins were gorged with blood. The pia was œdematous and, over the cerebellum, infiltrated with blood-stained fluid. The ventricles and brain substances appeared normal.

Microscopical examination. Sat. bichloride, 8 hours.

In the *XII cranial nucleus* there was very slight subdivision of chromatic bodies.

In the *X cranial nucleus*, *nucleus ambiguus*, and all the deeper cells in this region of the medulla there was extreme chromatolysis, with irregularity of cell outlines and frequent eccentricity of nuclei. The same conditions, rather less marked, were noted in all the other cranial nuclei. The nuclei in the cells of the *locus ceruleus* were invariably eccentric, often bulging. In most of the *Purkinje cells* the chromatic bodies were moderately subdivided. In the *motor cortex* there were some typical examples of central chromatolysis, but many of the giant stichochromes were entirely intact.

From the above cases it appears that uncomplicated acute lobar pneumonia may run a fatal course even with exaggerated nervous systems, without leaving uniform changes in the ganglion cells demonstrable by Nissl's method. In all the cases examined, the upper medullary nuclei were extensively altered, having lost most of their chromatic bodies, but the *nuc. XII* and the cells of the cord were not markedly changed or were practically normal, in uncomplicated cases.

In one case there was prolonged violent delirium while the cortical cells showed very slight lesions, irregularly distributed, and the majority of large cells appeared normal.

The ordinary temperature of fatal pneumonia (106°) appears not necessarily to leave any changes in the ganglion cells such as are seen in cases of sunstroke or in rabbits subjected to high temperature.

In the case of alcoholic pneumonia with terminal temperature of 109° the extreme bleaching of the cells recalls the very similar lesion in cases of sunstroke, but these changes are indistinguishable from those resulting from acute alcoholism and in this instance were possibly referable to the alcoholic element.

There seems to be no good reason to deny that there is an essential connection between the failure of the heart and respiration in fatal pneumonia and the changes in the ganglion cells of the medullary nuclei, and it seems probable also that the exaggerated activity of the cells is the determining factor in the production of lesions.

Diphtheria.—Pernici and Scagliosi [166] report the examination of the central nervous system in cases of diphtheria. In the *cortex* they found many normal cells, but some were much faded, very pale, and a portion of their protoplasm was entirely uncolored, while the nuclei were small, and the dendrites appeared granular. By Golgi's method such cells showed varicose atrophy. The changes in the cord were indefinite. Many of the cells appeared smaller than normal and their protoplasm was granular. The nuclei were often shrunken. A few cells had lost their processes and were reduced to a mass of coarse granules.

In guinea pigs killed or dying 5 to 22 days after subcutaneous injections of diphtheria cultures, Murawjeff [167] found in the anterior horn cells all grades of chromatolysis, reaching complete bleaching, and followed by degeneration, loss of nuclei, and vacuolation. The lesions were more marked in the lumbar than in the cervical cord.

The spinal ganglia were unaffected in four or five days. Many fibres in peripheral nerve trunks were degenerated.

In a later communication Murawjeff[168] reports that diphtheria anti-toxine causes very similar lesions in the nerve cells as does the toxine. When, however, the toxine and anti-toxine in neutralizing doses are injected simultaneously the nerve cells remain unaffected.

Acute Bronchitis, Asphyxia.—Male, 45 years. Had suffered repeatedly from attacks of bronchitis with spasmodic asthma. Brought to hospital March 10, 1897, breathing rapidly, very cyanotic, temperature 102°, with signs of severe general bronchitis. March 11, labored breathing and cyanosis continued without improvement, temperature 102.5°. March 12, all symptoms aggravated. March 13, died with extreme cyanosis, temperature 103.5°.

Autopsy 11 hours after death.

The blood was dark and fluid. The pleura and pericardium contained numerous ecchymoses. The lungs were intensely congested; the bronchi were thickly coated with muco-pus. The cerebral sinuses and pia were gorged with blood.

Microscopical examination.

In the *medulla*, the cells of the *nuc. XII* were usually normal in appearance. In the *nucleus X* and deeper lying cells the chromatic bodies were usually limited to a narrow peripheral ring, the remainder of the cell showing a more or less distinct chromatic network often infiltrated with yellowish pigment.

The same changes were very marked in the cells of the *corpora quadrigemina*. In the cortex the large cells showed a loss of chromatic bodies in a perinuclear or peripheral zone of variable extent. The chromatic network of the *arkyochromes* was regular and distinct.

In the *Purkinje cells* the chromatic bodies were usually of large size and regular contour, but deficient in number at the bases of the dendrites.

Septicæmia.—In this group are included five cases of general sepsis, including peritonitis, empyema, pyæmia, cellulitis.

Case I.—*Peritonitis.*—Male, 49 years. Had been excessively alcoholic. For four months before admission had

suffered from epigastric pain and marked tenderness, frequent vomiting of blood and occasional tarry stools, and had become excessively anæmic. Four days before death, he had sharp pain in the epigastrium, was prostrated, and died with symptoms of general peritonitis. The temperature remained about 101°. The last examination of the blood showed 10 per cent of hæmoglobin.

Autopsy 8 hours post-mortem. There was a circular ulcer of the duodenum which had perforated at one point directly into the peritoneal cavity. The peritoneum was everywhere the seat of a purulent inflammation and contained about one pint of free pus. There were evidences of chronic gastritis, fatty degeneration of the heart-muscle and liver, acute exudative nephritis, and extreme anæmia.

Microscopical examination. Lang's fluid.

In the *cord* many of the large stichochromes appeared normal or showed only a little raggedness of the chromatic bodies, probably of cadaveric origin. Others exhibited distinct signs of chromatolysis, either central or peripheral. In a few cells the chromatic bodies were all minutely subdivided.

The above description applies also to the cells *throughout the medulla*, although here the changes were slightly more general and distinct.

In the *cortex* most of the cells were very nearly normal, showing, with few exceptions, only slight subdivision of a few chromatic bodies, or slight irregularity of network. In the *Purkinje cells* the chromatic bodies were usually abundant, clear, and of normal size, but in a considerable number there was beginning subdivision of peripheral chromatic masses.

In nearly all regions there were frequent evidences of post-mortem change consisting in nuclear chromatophilia, diffuse staining, and vacuolation.

Case II.—*Empyema.*—Female, 22 years. Was delivered of a first child on February 24, 1897, after a dry labor of fourteen hours' duration, by forceps and craniotomy. Had been unwell for several days before admission when she had a temperature of 103.8°, and there was a fetid discharge from the vagina. After delivery she developed signs of pneumonia. The temperature ranged between 102° to 103° F. for twelve days; on March 11, following a chill, it rose to 105°, and just before death registered 107.2°. During the last eight days, there was mild delirium, with subsultus, nystagmus, unequal pupils, and on

March 11 the patient was in deep stupor. There was a purulent vaginal discharge from the first, continuing, with the uterus well involuted, until death, March 12.

Autopsy 8 hours post-mortem. There were two litres of thick fetid pus in the left chest, and an abscess cavity 4 cm. in diameter in the right broad ligament and uterine wall. The liver was very fatty. There was a moderate chronic nephritis. There were no signs of meningitis.

Microscopical examination. Sat. bichloride.

In the *cervical cord*, most of the larger cells appeared nearly normal, but some showed a slight raggedness or subdivision of the chromatic bodies. In the smaller cells the changes were more marked and the central areas of the cells were often bleached or diffusely stained.

In the *medulla* there were very general lesions. Some cells showed distinct "axonal degeneration." In others the fragmentation of chromatic bodies was uniform. Some of the larger cells appeared normal. In the motor cortex, nearly all the giant cells showed splitting or loss of chromatic bodies. None were completely bleached, and the cyto-reticulum was usually distinct.

In *Purkinje's cells* the chromatic bodies were uniformly deficient in size, very irregular in shape, and often greatly reduced in number.

Case III.—*Pyæmia.*—A well developed male infant was delivered by forceps, deeply asphyxiated, April 11, 1897. It never fully recovered from the asphyxia, being always feeble but nursing well, till on April 14th vomiting began. April 15th, there were hemorrhages from the naval and mouth, and "coffee-ground" vomitus; temperature 99.4°. These symptoms continued with a temperature 102.2°, when on April 17th, one wrist and hand became swollen and tender. On April 18th, the stools were tarry, and several indurated spots on the skin were noted. On April 19th, it died, previous temperature not taken.

Autopsy 6 hours post-mortem. The naval was sound. The right clavicle and shoulder joint, left forearm, occipital protuberance, both iliac bones and muscles, and left knee joint, were the seats of extensive abscesses, containing thin serous pus in which were large numbers of streptococci.

Microscopical examination. Lang's fluid.

There were everywhere evidences of post-mortem change consisting in nuclear chromatophilia, ragged granular aspect of chromatic bodies, and extensive vacuolation. The changes were extreme in the cortex, but slight in the medulla.

In the *cord* and *lower medulla* most of the large cells presented well-formed but, as is normal at this age, rather faint chromatic bodies. A few showed beginning central chromatolysis. Above the XII nucleus, especially in the deeper areas, most of the cells showed distinct powdering or complete loss of perinuclear or peripheral chromatic bodies. In some of the smaller cells neither network nor bodies could be seen. In this region cadaveric processes did not seriously interfere with the estimate of the above lesions.

In the *cortex* most of the cells contained considerable chromatic substance, but it was uniformly granular and distorted by vacuoles, as a result of decomposition. *Purkinje's cells* at this age are very small, and in this case they were entirely lacking in chromatic bodies.

Case IV.—*Diffuse Phlegmonous Inflammation.*—Male, 40 years. February 1st received a cut on the toe, which failed to heal. February 10th, he had a chill, with headache and vomiting, and was prostrated for a day, after which he went out and drank to excess. February 13th he noticed pain and swelling in the knee joint and was again prostrated.

On admission February 18th, there was gangrene of left great toe, acute arthritis of the knee joint, and diffuse cellulitis of the thigh. Feb. 19, temperature 105°, about which point it remained. Incision had no effect in limiting the inflammation, although large quantities of pus were evacuated at various times. February 28th, the patient developed delirium and stupor which persisted till death. The general septic condition was extreme during the last three weeks of the illness and the temperature remained about 105° till death, March 25th.

Autopsy 22 hours after death. Body emaciated. There was gangrene of foot, purulent arthritis of knee, and the muscles of the thigh were largely obliterated by an enormous sacculated pus cavity. There were no gross visceral lesions of importance.

Microscopical examination.

In the *cord*, most of the cells contained the usual number of chromatic bodies, but in a considerable number they were partly subdivided, and in some were finely powdered and, in a few segments, usually perinuclear, were lacking. The cyto-reticulum remained.

In the *IX, X and XII cranial nuclei*, most of the cells showed many well-formed chromatic bodies rather faintly staining. Many deeper cells, however, contained only

two or three well-formed chromatic bodies, the remainder of the cell body being bleached. A few cells were entirely bleached.

In the *olives* and *external arcuate nuclei* the chromatic substance was granular but abundant.

In the *motor cortex*, advanced lesions were rather rare, but some of the giant cells exhibited marked changes, the centres being bleached, the peripheries containing a ring of granules, and persisting chromatic bodies being markedly subdivided. The chromatic network of the cortical arkyochromes was often irregular, granular, and partially faded.

The majority of *Purkinje's cells* presented ragged subdivided chromatic bodies, often very deficient in number. Some cells, however, contained well-formed bodies in normal number and arrangement.

No distinct nuclear changes could be detected in the cells in this case.

Case V.—*Pulmonary Tuberculosis. Tuberculous Nephritis. Acute Cellulitis.*—Male, 35 years. Had suffered from cough and dyspnœa for one year, and œdema of legs for two weeks. September 18, 1896, temperature 101°. Signs of tuberculosis of both lungs. Urine, s. g. 1022. No albumen. September 23d, was delirious, temperature 102°. September 24th, a large diffuse phlegmon developed in upper right arm; delirious; temperature 105°. September 25th, urine moderately diminished, slightly albuminous; temperature 105°. September 27th, delirium and coma; involuntary stools; temperature 102°. September 28th, died; temperature 108°.

Autopsy four hours after death. There were many old and fresh tubercles in both lungs. No pneumonia. A few small cavities. Many miliary tubercles were scattered throughout the kidneys of which the surface was smooth, capsule free, and markings very irregular. The soft parts of the upper arm were extensively infiltrated with pus. The pia was very œdematous.

Microscopical examination. Lang's fluid.

Throughout the *medulla* there is extreme chromatolysis. In the *nuc. XII*, the chromatic bodies are reduced to fine granules or appear as irregular masses limited to the sides or poles of the cell, while some of the cells are moderately bleached. Most of the superficial cells throughout the floor of the fourth ventricle are in the same condition. In the *nuc. X*, *IX*, *VIII*, *V*,

IV, III, many cells are entirely bleached, but most of them retain a little granular chromatic detritus. In some deeper lying groups of cells there are no traces whatever of chromatic substance. Usually the cyto-reticulum is distinctly visible. In the cerebellum *Purkinje's cells* are either completely bleached or retain a very few slender chromatic bodies. In the *cortex* the larger cells show very little chromatic substance and some are entirely bleached. In the smaller arkyochromes the chromatic reticulum is usually distinct. In all regions the nuclei contain many small secondary nucleoli.

Summary of Observations on Cases of General Sepsis.—In the foregoing cases of general septicæmia, considerable alteration in the chromatic structure of the nerve cells was observed in each instance. These lesions were very irregular in degree and distribution, some regions, especially the cord, cerebellum, and cortex being often very slightly affected. The medullary nuclei were most seriously damaged. There appears to be a fairly constant parallel between the grade of chromatolysis and the severity and duration of the toxæmia and the height of the temperature. That local conditions have a determining influence in the occurrence of these lesions appears from the fact that adjoining nuclei and contiguous cells were very differently affected.

Tetanus.—Most of the studies of the lesions of the central nervous system in tetanus, by means of Nissl's method have appeared within the past two years and the evidence presented is so fragmentary and incomplete that it is at present impossible to determine what special cellular lesions are to be referred to the action of this particular toxæmia.

The first studies of the cellular changes in experimental tetanus were reported by Beck,[169] who examined the cord of two rabbits, dying four days after inoculation with a culture of tetanus. The examination, evidently conducted

with care and judgment, indicated as the cellular lesion referable to the infection. 1st. Swelling of the cell body and separation of the chromatic masses. Often the chromatic bodies were swollen or apparently fused together. 2d. Very often the cells showed a partial peripheral loss of chromatic substance, which the author refers to a degenerative process limited to the area of origin of the axis-cylinder process. 3d. In one of the rabbits the changes were more advanced and most of the cells were swollen, the chromatic structures had largely disappeared, and the cell body stained diffusely blue.

Beck was not convinced that any of these changes were specifically related to tetanus, but regarded them as very similar to those noted by other writers in experimental toxæmias.

Marinesco[170] killed three guinea pigs in rather short periods by injection of tetanus toxine, and examined the cords by Nissl's method. There were numerous hemorrhages in the gray matter. The chromatic bodies were thinned and shortened, and sometimes reduced to a series of granules scattered irregularly throughout the cell body. Occasionally there was peripheral chromatolysis. In advanced stages the chromatic bodies disappeared entirely. The achromatic substance was diffusely stained, and some cells appeared quite homogeneous and darkly stained. In the earlier stages of the toxæmia, very slight alteration could be noted.

Claude[171] produced a subacute myelitis with cachexia, by injections of tetanus toxine, killing the animal after six weeks, but it does not appear that the condition induced could be considered a fair example of experimental tetanus.

Courmont, Doyon and Paviot[172] report the examination

of the cords of three guinea pigs, dying 12 hours, and 9 and 10 days after receiving injections of tetanus toxin. Some of the cells of the anterior horns were found transformed into "deep blue masses" but no other changes were observed. In the cord of a normal guinea pig similar cells were found.

In the cords of three dogs dying five, six, and fourteen days after the injection of tetanus toxine, the anterior horn cells were found entirely normal. On these data the authors deny that tetanus produces any cellular lesions in the spinal cord and attempt especially to discredit the observations of Marinesco and Claude.

Unfortunately the sections in these cases were cut by a razor.

In June, 1898, they presented before the Paris Society of Biology,[172] microscopical specimens claimed to demonstrate the following conditions:

1. In the cords of five dogs suffering from tetanus, "tetaniques," there were no appreciable cellular alterations.

2. In the cords of guinea pigs killed during the period of localized spasms, cellular lesions were present but they were scattered and bilateral, and showed no relation to the seat of the spasms.

3. In the cord of a guinea pig cured of tetanus and killed on the forty-fifth day, the lesions were much more intense than in the preceding cases and affected almost all the cells.

The importance of these observations it is impossible to estimate in the absence of a detailed report, which is promised, in a later number of the same journal (July, 1898).

Goldscheider and Flatau[173] have reported an extensive study of the changes induced by tetanus on the spinal

stichochrome of the rabbit. These changes were found to be uniformly present and consisted in swelling of the nucleolus, cell body, and chromatic masses, followed by granular disintegration of the chromatic bodies. The simultaneous injection of anti-toxine retarded both the appearance of symptoms and the occurrence of changes in the ganglion cells. They believe that a strict parallel between the cellular lesions and the symptoms following injections of tetanus toxine is not to be found. A close examination of the details of their report fails, however, to show that there is any serious discrepancy between the grade of cellular change and the severity of symptoms, although the parallelism is not uniformly maintained at all stages.

Pechoutre[174] found, in rabbits killed four days after injection with cultures of tetanus, the same lesions in the anterior horn cells as described by Beck, and Goldscheider and Flatau.

Hunter[175] examined the spinal cord in two cases of rapidly fatal (24 hours) tetanus. In one he noted a disappearance of the chromatic bodies, and a uniformly homogeneous appearance of the ganglion cells.

In the second case, complicated by extensive pneumonia, the ganglion cells of the cord appeared normal.

It does not appear that the author examined the cells of the medulla or brain in either case, a failure which forbids the drawing of any deductions from these cases, regarding the cellular lesions of tetanus in the human subject.

Goebel[177] reports the examination of the anterior horn cells in a case of tetanus in the human subject. In these cells the nucleus had often lost its outline while the cell body remained normal. Many cells showed great irregularity in form and arrangement of the chromatic bodies,

while some had lost their processes and nuclei, and were reduced to a mass of pigment grains in which only traces of the chromatic substance could be detected.

Goldscheider and Flatau[176] describe the changes in the ganglion cells of the cord in two cases of tetanus. In one, the course of the disease was prolonged to five days, and the changes in the cells consisted in almost complete disappearance of chromatic bodies. The nuclei was lightly but diffusely stained, the nucleoli were not swollen, but rather reduced in size. The patient had few convulsions, and the ante-mortem temperature rose to 39.9° only.

The second case was more rapidly fatal, with severe convulsions. Ante-mortem temperature not stated. Here the cellular lesions consisted only in swelling and partial bleaching of the nucleolus, and in swelling of the chromatic bodies, without distinct bleaching.

Westphal describes similar changes in the anterior horn cells in a more protracted case of tetanus. (Fort. der Med., 1898, p. 483).

The writer's series includes one case of tetanus. The patient was a boy of 19 years. The duration of his entire illness was five days; of severe symptoms, three days. The temperature was but slightly elevated until shortly before death when it rose to 107°. The tonic spasm was neither very severe nor continuous, but the fatal termination was marked by several severe general tonic and clonic convulsions. The mind was not greatly affected until the end when, between the convulsions, the patient remained comatose or delirious.

Autopsy one hour after death. There was noted a characteristic bluish discoloration of the gray matter throughout the brain and cord. There were a few ecchymoses on the outer edge of the optic thalamus. There was considerable œdema, but no hyperæmia of the pia. The viscera showed the lesions of the "status infectiosus." The brain and cord were fixed in 97 per cent alcohol. The most marked cellular changes were found in the *cortex*, and consisted in uniform and usually complete

chromatolysis, without distinct alterations in nucleus or achromatic substance. These changes affected especially the archystichochromes and giant stichochromes, nearly all of these cells presenting an appearance quite indistinguishable from that seen in cases of sunstroke and mechanical obstruction to cerebral circulation. In the *medulla* the superficial nuclei showed very slight but general chromatolysis, but the deep nuclei were much altered, many showing complete chromatolysis and marked eccentricity of nuclei. Many *Purkinje cells* showed advanced chromatolysis, others exhibited moderate granular subdivision of chromatic bodies, especially marked in the peripheries and in the dendrites. The *spinal stichochromes* nearly all showed evidence of chromatolysis. In some instances the chromatic bodies appeared swollen and pale as described by Beck. Swelling of the nucleolus was not noted as a distinct feature. Many spinal stichochromes were reduced to the homogeneous appearance characteristic of the cortical cells. The capillaries were everywhere distended with blood and a few minute extravasations were found in the floor of the fourth ventricle. To this general condition the writer believes the cellular lesions are partly referable.

From the evidence at hand, it appears that the earliest cellular lesions in tetanus consist, as originally described by Beck, in swelling of the chromatic bodies, and cell body, and probably also of the nucleolus; that these initial changes are rapidly followed by progressive chromatolysis which may reach an extreme stage without serious alteration of the achromatic substance or nucleus; that these lesions are of rather irregular distribution, being more uniform and intense in the brain than in the cord, and with the possible exception of the early stages, the changes are not specific of the disease.

The writer cannot agree with Goldscheider and Flatau in their supposition that the stages of extreme chromatolysis are referable to febrile disturbances, nor does the failure of some writers to find cellular lesions in the spinal cord in tetanus seem to diminish the importance of the

considerable number of positive results now available. The chief imperfection in previous studies of this condition lies in the failure to examine the entire central nervous system, as the writer's case indicates that the chief cellular lesions are located in the cerebral cortex and medulla.

Hydrophobia.—The cellular lesions demonstrable by older methods in hydrophobia have been fully described by Schaffer[178] and others, while the subject of the pathology of rabies has been ably reviewed by Hogyes[179].

Nagy[180] was apparently the first to employ Nissl's method in this study. During the first four days after infection with rabies in animals, Nagy found that the chromatolytic changes in the cord and brain were not extreme nor were all portions of the cell affected. With the onset of fever, and nervous symptoms, (fifth to seventh day) the changes became general and pronounced. In the stage of paralysis, many completely degenerated cells were found throughout the brain and cord. The changes were most advanced in that part of the cord to which the virus first gained access, as in the lumbar cord when the infection occurs in the sciatic distribution. The lesions described consisted in granular disintegration of the chromatic bodies, followed by homogenization of the cell body, vacuolation, loss of nuclei and processes, and terminal atrophy.

Later, Nagy[181] found that the administration of antirabic serum prevented both the symptoms and the changes in the nervous system following infection with the virus.

Babes[72] has described in hydrophobia experimentally induced in rabbits, extreme stages of chromatolysis, deep staining of the achromatic substances, vacuolation, and rupture of dendrites. In some cells peculiar spindle-

shaped or polygonal areas in the cell body were marked off by clefts and fissures. In the nuclei he observed the loss of nuclear membrane, compression by perinuclear vacuoles, swelling and disappearance of nucleolus, and granular disintegration of all nuclear elements.

Sabrazes and Cabannes[182] have examined by Nissl's method the cervical cord of a case of rabies in a man, 37 years of age. The lesions were most marked in the posterior horns and posterior median portion of the anterior horns. Most of the cells in these regions were completely bleached and had lost their processes. In the anterior horns a variety of the earlier stages of chromatolysis were noted, and nuclear changes were prominent.

The present series includes one case of hydrophobia in the human subject. The patient was a girl aged 19 years, who died four days after the development of the disease with very typical signs of this malady. It was impossible to determine the period of incubation. The cerebral symptoms were very marked throughout the illness, the delirium being violent and terminating in coma. Twenty-four hours before death the temperature, previously little elevated, rose to 105°.

At the autopsy, eight hours after death, the viscera presented the usual changes of the "status infectiosus." The gray matter throughout the central nervous system exhibited in an extreme degree the deep cyanotic color, which is characteristic of both hydrophobia and tetanus. There was also marked congestion of the larger veins of the central nervous system, but no ecchymoses were discovered. Intra-peritoneal and intra-meningeal inoculations from the medulla, made by Dr. Chas. Norris, reproduced the disease in typical form in several series of animals.

Microscopical examination. (Van Gehuchten's fluid, 22 hours. Alcohol).

The cells throughout the *spinal cord* and *spinal ganglia* showed uniform diffuse chromatolysis more marked centrally, often with eccentricity of nucleus. The nucleoli were usually much swollen; the nuclear membrane usually invisible in specimens stained by methylene blue alone, but sometimes demonstrable, in swollen condition,

by erythrosin. The achromatic envelop of the spinal stichochromes stained rather deeply with methylene blue. The borders of the cells and processes were often ragged.

Throughout the medulla the lesions were of the same character, but more intense. All the large stichochromes were extensively altered. The raggedness of the cell borders and processes, the loss of nuclear membrane, and the apparent destruction of the underlying cyto-reticulum were very distinct characters in many of these large medullary stichochromes.

In the *cortex* there was a uniform but not extreme loss of chromatic substance, these regions being considerably less affected than the medulla and cord.

In the cells of the *motor cortex*, there was considerable subdivision and irregularity of the chromatic bodies and network, most advanced about the nucleus and giving these cells, in sections 10 μ in thickness, a somewhat diffusely stained appearance. A similar condition rather more marked was observed in the *Purkinje cells*. Vacuolation of the nucleoli was an extremely pronounced change in nearly all the nerve cells throughout the central nervous system.

Besides the cellular lesions the features of the case were the extreme congestion of the gray matter, everywhere accompanied, especially in the medulla, by many small hemorrhages. There was no distinct circumvascular infiltration with round cells.

Bubonic Plague.—In experimental pest (bubonic plague) Babes[182] found very extensive cellular lesions, consisting in complete chromatolysis, vacuolation, destruction of the peripheral portions of the cell body, and loss of nuclear membrane. Bacilli were often seen within the cell body. The lesions varied with the strength of the injected material. In very rapidly fatal cases, the changes were limited to the cells and were usually of less advanced type. In slower cases, vascular changes became prominent, and cellular lesions had progressed further.

Lugaro[183] has also reported and fully described, in the same infection experimentally induced in animals, extensive lesions in the chromatic and achromatic substance and in the nuclei of the nerve cells, very similar to those described by Babes.

In young children dying with or without fever from the toxæmia of *acute intestinal lesions*, Muller and Manicatide[184] found many advanced changes in the nerve cells. These consisted chiefly in swelling, irregularity in outline, and partial or complete bleaching of the chromatic bodies. In some foci the cells had lost their normal outlines and dendrites were missing. Nuclei and nucleoli were often misplaced and the nuclei usually stained darkly. The lesions were found in both brain and cord. The authors considered them in no respect specific.

In *leprosy* Babes[172] has verified Soudakievicz's domonstration of the *bacillus leprœ* in cells of the spinal ganglia and anterior horns, and describes the appearances of the cells harboring these germs. In many instances the infected cells were very little changed, the chromatic structures being practically intact. In other cells there were vacuoles in the protoplasm and the nuclear membrane was sinuous or lost. In still other cells the bacilli lay in a mass of pigment, while the cells had completely lost all chromatic bodies, were extensively vacuolated, and the nuclear membrane had disappeared.

Pernicious Malaria.—In a case of pernicious æstivo-autumnal malaria, the nervous system was examined by Nissl's method.

The patient, male, 64 years, without previous illness, began to suffer from mild, irregular chills and fever October 1, 1895. Cerebral symptoms were noted early in the illness, in the form of headache, drowsiness, and occasional stupor. During the three weeks of his illness in the hospital, he remained nearly constantly in mild stupor, broken by periods of partial consciousness or active delirium. Treatment, bromides, quinine, and arsenic. The blood contained an unusually large number of parasites which, however, largely disappeared the day before death, which occurred October 25. The temperature ranged continuously from 101° to 104°, reaching 108° just before the fatal termination.

Autopsy eight hours after death. Some bone lesions probably of syphilitic origin were discovered. Otherwise the lesions were those of pernicious malaria. The brain and meninges were moderately œdematous.

Microscopical examination showed a moderate deposit of malarial pigment in the blood vessels and in their walls. The large cells of the cord and medulla showed a moderate grade of general chromatolysis. In some of the medullary ganglia these changes were extreme and the chromatic substance was reduced to a few fine pale granules or rarely was entirely absent. The appearance of Purkinje's cells was somewhat characteristic in that the chromatic bodies at the bases of the cells was intact and of large size, while in the region of the dendrites they were minutely subdivided or entirely absent. Throughout the cortex the cells showed no marked changes other than a uniform deficiency in quantity of chromatic substance.

In all parts of the nervous system not excepting even the Purkinje cells there was an extensive deposit of yellowish granular pigment of the usual character (not malarial) and distribution.

Section VI.

The Significance of the Chromatic Bodies.

The evidence regarding the significance of the chromatic bodies of Nissl is furnished by the study of their usual morphology, their probable chemical composition, their morphological changes at different periods of the life of the cell, their variations in physiological states, and their behavior under pathological conditions.

The foregoing consideration of some of these topics shows that the chromatic substance may assume a great variety of appearances from a large, granular or partly homogeneous circumscribed mass to a diffuse infiltration of the cytoplasm and possibly also of the nucleus.

This fact, especially when viewed in the light of Held's researches, indicates that we are dealing not with a fixed and formed histological element of the cell, but with a

fluid or semi-fluid chemical constituent, occupying of course a certain space, but well limited by the achromatic elements. The observation emphasized by Lenhossek[188] that there is yet strong uniformity of appearance in the chromatic bodies in similar situations, throughout the vertebrate series, does not tend seriously against this view, for as noted by Lugaro[46] the chromatic substance appears to passively adapt itself to the structure of the achromatic portion of the cell. It is difficult or impossible to find any parallel instance where a distinct histological element of the normal cell suffers such remarkable changes in morphology.

The chromatic substance of the nerve cell appears to be more comparable in these respects to the hæmoglobin of the red corpuscles of the blood or to the pepsinogen of the peptic cells, than to cytoplasm, spongioplasm, nucleus, nucleolus, centrosome, or other recognized histological element of the cell.

The morphology of the chromatic bodies at different periods of the life history of the nerve cell, furnishes evidence of a similar character, and indicates also that the chromatic masses are a feature of the fully developed functionating cell, but are not essential to its partial activity.

Reference has already been made to the observations of Vas[70] that the "Nissl bodies" are wanting in the sympathetic ganglion cell at the seventh month, and are not fully developed until the eleventh year, and to that of Eve[73] who finds that only the vagi nuclei in the rabbit's embryo, 2.5 in. long, contain chromatic masses. In the spinal and medullary stichochromes of new born infants examined by the writer, the chromatic masses were less numerous and much paler than in the adult cells, while Purkinje's cells failed to show any distinct traces of such bodies. In

the senile ganglion cell the increasing deposit of pigment is greatly to the cost of the content in chromatic substance, and at this age, nervous functions are generally less active.

The comparative morphology of chromatic bodies in various vertebrates, in so far as this field has been investigated, indicates that the higher the development of the cell the more abundant and distinct are the chromatic bodies. Colucci finds the same rule to hold among the various cells of the human organism, although he regards the chromatic bodies as fixed elements of the cell.

Comparing the spinal stichochromes of man, the dog, the cat, and the rabbit, with those of the sluggish mud puppy and water moccasin, the writer finds that the motor cells of the more active animals show a greatly superior development of chromatic substance. The extensive study of Levi[189] on the comparative morphology of nerve cells in vertebrates leads to the same general conclusion.

It may, therefore, be readily seen that there is abundant theoretical evidence for the belief that the chromatic substance is principally related to the activities of the cell, and from that standpoint numerous studies have been undertaken to ascertain the behavior of the nerve cell and especially of its chromatic elements in physiological conditions.

Effects of Fatigue Upon the Nerve Cell.

Among the earliest of these studies was that of Hodge.[190] This experimenter resorted to electrical stimulation of the cervical sympathetic ganglion for several hours, allowing short intervals of rest to the animals, dogs, which usually died before the experiment was concluded. He used the ganglia of the opposite side for control preparations. The changes noted consisted in a marked decrease

in the size of the nucleus, with irregularity in its outlines, loss of its clear reticulated appearance, and a darker staining tendency. The cell body was shrunken and vacuolated and the pericellular lymph space was dilated. No observations were reported on the chromatic substances.

About the same time, and with a similar object, Mann[191] studied the change in nerve cells during functional activity. After working dogs to the point of physical fatigue, and later to exhaustion, he examined the cortical brain cells by a method similar to Nissl's. In the normal brain the cells appeared as dark blue bodies on a light background, while in the brain of the exhausted animal, they appeared very pale or quite colorless. This difference in color he refers to the withdrawal of lymph which he supposes is more abundant in the active cell. He further concludes; that during rest several chromatic principles are stored up in the nerve cell, which are consumed during functional activity; that activity is accompanied by increase of size of body, nucleus, and nucleolus, of motor, sensory, and sympathetic ganglion cells, while fatigue is accompanied by a shrivelling of the nucleus and probably also of the cell, and by the diffusion of chromatic material in the nucleus.

Serious errors in the procedures and technics of both Hodge and Mann have been pointed out, greatly lessening the value of their studies.

It is difficult to see any similarity between normal activity of the sympathetic ganglion and prolonged electrical stimulation of this structure, nor does it appear probable that prolonged physical exertion could greatly alter the cortical brain cells of the dog. Nissl[192] therefore thinks that all the unusual appearances seen by Hodge and Mann were artifacts, a criticism rather too severe,

since the trustworthy investigations of Lugaro[200] have demonstrated changes in the volume of nucleus and nucleolus as the result of exhaustion, and several years previously, Korybutt and Daskiewicz[193] after electrical stimulation of the sciatic, had found marked increase in size of the nuclei of the spinal cells giving origin to this nerve.

Vas[70] also faradized the upper cervical sympathetic ganglion of the rabbit for fifteen minutes, and found thereafter that the nucleus was enlarged, eccentric, often bulging from the periphery of the cell. The cell body was increased one-third in size. The perinuclear zone was bleached and poor in chromatic substance, while a ring of large chromatic bodies remained along the periphery of the cell.

Lugaro[200] discredits the importance of these findings, because Vas dissected the ganglia while the animal was still living, thus subjecting it to extreme traumatic influences, while Nissl criticises the use of electricity as a wholly unsuitable means of exciting functional activity in ganglionic cells.

Lambert[194] after exposing the sympathetic ganglia of rabbits and applying galvanism for fifteen minutes, found marked eccentricity of the nucleus. Unfortunately, he killed the animals by hydrocyanic acid.

Levi,[195] after electrical stimulation of the spinal ganglia in rabbits, found no change in the chromatic granules, but found an increase in the size and number of the fine granules staining by fuchsin which lie among the fibrils in the achromatic portion of the cell. He believes also that during cellular activity there is an increase in the size and number of the granules of true chromatin lying about the nucleoli of these cells.

Eve,[73] studying the sympathetic ganglion cells in prolonged activity and in repose, finds that the chromatic bodies disappear, the cell staining diffusely pale blue, after galvanization of the ganglia or their nerve trunks, changes similar to those occurring in the spinal stichochromes after strychnine poisoning. Eve supposes that cellular activity produces acid metabolic products that dissolve the chromatic bodies. He discovered in the nuclei no changes referable to fatigue.

To Magini[196] belongs the credit of calling attention to the electric lobe of the torpedo, as a specially favorable situation for the study of changes in ganglion cells, referable to fatigue. The adult torpedo when killed in a healthy condition reacts with well known violent electric discharges. According to Magini the nuclei of the governing cells of this organ then show, without exception, marked eccentricity, being always drawn toward the electric nerve, while the nucleolus is always found close to the nuclear membrane. When the adult animal dies slowly out of water, it does not discharge electricity, and the nuclei are not found drawn toward the nerve or the nucleoli toward the nuclear membrane. Very young torpedoes do not give electric discharges, and the nucleoli of the rudimentary cells are always found in the centre of the pale nuclei. No references to the chromatic substance was made in Magini's observations. Coggi,[197] who saw these specimens, as well as Valenza[198] and Lugaro, regard this eccentricity of the nucleus as an artifact.

Valenza[198] applied strong faradization to the electric lobe of the torpedo. In the cells nearest to the electrode there was hyperchromatosis of the nucleus and shrinkage of the cell body; in the more distant cells there was swelling of the cell body and hyperchromatosis of the periph-

eral zones. By direct cauterization of the organ there was produced hyperchromatoses of the nucleus and a concentration of chromatic bodies about it.

Valenza found no changes referable to simple activity or repose.

Nissl, 1896,[199] reviewing the results of this line of study up to date, concluded that the morphology of the nerve cell in exhaustion was still undetermined, and that the evidence was still insufficient to show whether the pyknomorphous condition of the cell is the expression of the resting state or the apyknomorphous condition the expression of activity. Since that time there have appeared the careful studies of Lugaro[200] who still fails to discover chromatic changes referable to fatigue. Lugaro excited the cervical sympathetic ganglia by faradic electricity, killed the animals before further manipulation of the ganglia, and carefully observed the changes, resorting to exact measurements of the cell body, nucleus, and nucleolus. His conclusions are as follows: "Activity of the nerve cell is accompanied by a state of turgescence of its protoplasm, while fatigue produces a progressive diminution in size of the cell body. In moderate degrees of fatigue, while the cell body swells, the nucleus does not change its volume. The shape of the nucleus always remains uniform, nor is its position changed, marked eccentricity being just as common in ganglia in repose as in fatigue. When activity is much prolonged, the nucleus undergoes the same changes in volume as the cell body, but less markedly, and more slowly. The quantity of chromatic substance in the cell body varies as an individual character, and in relation to the size of the cell. During the swelling of the cell in activity there is perhaps an increase of chromatic substance, and in the stage of fatigue,

perhaps it fades a little and becomes more diffuse, but it is certain that the great differences in staining power and content of chromatic substance that one sees in cells of the same ganglia cannot be attributed to differences in physiological state. Activity and fatigue may cause changes in the staining capacity of all sorts of cells, but do not change a pyknomorphous into an apyknomorphous cell. Activity determines in the nucleolus an increase of volume which yields slowly to the contrary action of fatigue."

The interesting studies of Pergens[201] on the effects on the retinal cells of strong illumination do not seem to bear directly on this subject. Among other changes, however, Pergens noted a diminished affinity for basic dyes in the nuclei and bodies of the rods and cones.

It will thus be seen that the numerous foregoing studies have failed to establish a connection between the chromatic substance of the nerve cell and its conditions of activity or fatigue, so far as can be determined after direct electrical stimulation.

Nissl's objection that electrical stimulation cannot be substituted for natural cellular activity, but works as a traumatic or chemical irritant, seems most reasonable, and indicates that any such studies should be undertaken on different principles.

Accordingly, Pick[202] has recently devised a method of securing specimens of exhausted nerve cells, which is apparently free from any of the objections raised against previous methods. He exposed the motor cortex of one side in monkeys and cats, applied faradism for one hour, exciting muscular contractions of the limbs of the opposite side only. The fatigued cells examined were those of the cord, and in this region he found that the cells of the

convulsed side presented marked granular subdivision of the perinuclear chromatic bodies, and shrinkage and diffuse staining of the nucleus. Not only were the anterior horn cells affected, but the lesions were most advanced in the cells lying midway between the anterior and posterior horns. This fact Pick regards as further evidence that the anterior horn cells are not directly connected with the cortical neuron but are separated by a second intermediate neuron.

Luxenburg[203] has also recently reported a somewhat similar study leading to very similar conclusions.

If corroborated, Pick's and Luxenburg's results would seem to furnish the long expected evidence that natural fatigue of the ganglion cells is associated with a loss of chromatic substance in the nerve cell.

Superior to all the results obtained by experimentation appears to be the isolated and too little considered observation of Levi,[204] that in *some animals the chromatic bodies disappear from the spinal stichochromes during hibernation.* Such a fact, if corroborated, must carry very great significance concerning the relation of chromatic substance and cellular activity. The writer has made several attempts to secure animals in a state of hibernation, but has so far been unsuccessful.

Relation of the Chromatic Bodies and the State of Nutrition of the Cell.

A further line of investigation has had in view the allied theory that the chromatic bodies are reserve nutritive substances stored in the cell, to be used up during periods of activity, in other words, that they represent the potential energy of the cell. This theory has been rather eagerly accepted by many French writers, and Marinesco[205] has

accordingly suggested the term *kinetoplasm* for the chromatic substance and *trophoplasm* for the achromatic part of the cell.

Numerous attempts have been made to alter the conditions of nutrition surrounding the nerve cell in the hope of establishing a connection between the state of the blood and lymph supply of the cell, and its content in chromatic substance.

Monti's[206] experiments are the first bearing indirectly on this point. He produced multiple emboli of the cerebral vessels by intravenous injection of powdered lycopodium, and found, by Golgi's method, that within a few hours varicosities were produced in the dendrites lying next the small thrombosed vessels, while the dendrites in contact with pervious vessels remained normal. These changes gradually approached the cell body, until, in 48 hours, the cell body began to show alterations.

These experiments were repeated by Lamy,[207] who examined the cells by Nissl's method, and found progressive loss of chromatic substance beginning in the altered dendrites and gradually affecting the entire cell body. These changes were similar to those produced in the lumbar cord by ligature of the aorta.

This latter method of affecting the nutrition of the ganglion cell was first employed by Sarbo[208]. In one and one-half hours after tying the abdominal aorta, the chromatic bodies of the spinal stichochromes were less distinct and their outlines less sharp, while the nucleus stained diffusely pale blue. In 24 hours nearly all cells were affected. The chromatic bodies throughout the cell body and dentrites were broken up into a series of fine particles, although some cells showed apparently normal segments. The nuclei presented characteristic alterations which he

denominated "acute homogenization with atrophy." They stained diffusely deep blue, the nuclear membrane being invisible, and the nucleus appeared to be reduced in size. In some instances the nucleus showed advanced changes while the cell body and dendrites contained nearly normal chromatic bodies. A second form of alteration he describes as "homogeneous swelling," in which the body is enlarged, uniformly darkened, and filled with fine granules. In some cells, also, a process of partial sclerosis affected segments of the body which appeared very dark, as though several chromatic bodies had become fused together. Vacuolation of these altered cells was often marked.

Juliusberger[40] also, compressed the abdominal aorta in rabbits, and at the expiration of 15 to 60 minutes, found a granular disintegration of the chromatic bodies progressing concentrically from the perinuclear zone, or affecting smaller segments only.

Marinesco,[209] repeating these experiments, concluded that anæmia does not always produce similar lesions. As a rule, disintegration of chromatic bodies began in his cases in the dendrites, and progressed toward the nucleus, being well marked usually in six hours. He found many swollen cells. In some instances the chromatic bodies appeared to be massed together and the achromatic portion deeply stained.

The results of these experimental studies are very fully verified in the human subject by the writer's cases of thrombosis of cerebral vessels and cerebral hemorrhage. In no other group of cases was the destruction of chromatic substance so rapid and complete, and it seems reasonable to conclude therefrom that the chromatic structures of these nerve cells are more immediately affected by changes in their blood supply than by any

other influences whose effects upon them have yet been studied.

Moreover, throughout all groups of cases in the present series, there was constantly recurring evidence that previous overaction of the nerve cells, as well as local disorders of circulation, were of prime importance in determining the distribution of the lesions in the various toxæmias.

It would seem also that the demonstration of the close dependence of the chromatic bodies upon the blood supply of the cell had furnished the true answer to the question which Hodge, Mann, Lugaro, and others, had in view. For even if it were possible to induce a state of complete natural fatigue in the nerve cell, it might still be difficult to determine which element of the cell were most concerned with such activity, if the normal sources of its supply were still open. All of these considerations indicate, therefore, that the chromatic bodies constitute surplus nutritive products of the nerve cell, or represent potential energy in the cell.

Against such a view Colucci,[210] however, expresses himself very positively. He finds no reason to suppose that the nutritive function of nerve cells is so entirely different from that of other cells as to require the storage of large masses like the chromatic bodies. He regards it as unreasonable to suppose that a nutritive substance should be found so polymorphous and yet, in similar situations, so orderly and fixed as are the chromatic bodies. For a nutritive substance ought to be found about the nucleus where most work is to be done and not limited to the periphery as in many cells, or found in the dendrites. He calls attention to the fact that there is no uniform quantitative relation between the chromatic bodies and

the achromatic substance, one being abundant where the other is often lacking.

Nevertheless, the consideration of more recent data leads irresistibly to the conclusion that *the chromatic bodies of the nerve cells represent a state of physiological nutrition, and may vary between their full development in the anterior horn cells of the adult lumbar cord and their temporary absence in the cells of the hibernating animal.*

The Functional Capacity of Cells Deficient in Chromatic Substance.

It remains to determine how far the loss of this nutritive material affects the functional activity of the cell.

On this point, it is to be admitted at once that the functions of vital nerve centres may be entirely destroyed without leaving demonstrable changes in the chromatic structures, as in the cases of rapidly fatal poisoning, and in this respect the original expectations of Nissl's stain have been disappointed.

On the other hand, the unbiased observer will admit from the reports of the condition of the cells in the many pathological conditions in which Nissl's method has been employed, that there is a fair general parallel, subject of course to a great variety of limitations, between the extent of the lesions in the chromatic structures and the grade of functional disorder, in the ganglion cells. The exceptions to the above rule are so frequent, however, as to render it equally apparent that the capacity of a cell to maintain a temporary function cannot always be estimated by the condition of its chromatic elements.

Of special interest are the contributions recently made to this subject by Goldscheider and Flatau[211].

These investigators employed two very successful

methods of altering the conditions of the chromatic substance in the anterior horn cells. First, they injected into the ear veins of rabbits repeated doses, .005 to .01 gr., of malonitril ($CN—CH_2—CN$), producing thereby marked symptoms of poisoning, dyspnœa, salivation, convulsions, and paresis, and at the height of the symptoms rapidly restored the animals to apparently their normal conditions by injections of Na sub-sulphate. This latter substance has been shown by Heymans and Masuin[212] to be a direct chemical antidote to malonitril. The chromatic bodies of the spinal stichochromes after the administration of malonitril in poisonous doses, showed irregularities of outline and occasionally subdivision into fine granules. The spindles in the dendrites usually remained normal. The nuclei and the achromatic portions of the cells were diffusely stained. After restoration of the animals by Na sub-sulphate, similar changes in the chromatic bodies were found to persist for some hours although the motor power of the animals was apparently restored.

Secondly, rabbits were placed in a thermostat at a temperature of 45° C. until their internal temperature was elevated to 42° to 44° C., a procedure which induced dyspnœa, great weakness, spasms, and convulsions. In these animals the spinal stichochromes showed a complete absence of chromatic bodies. This change was noted in the periphery of the cell when the temperature of the animals reached 41° to 42° C., and became general when the temperature rose to 43°.

When the animals were allowed to recuperate in the open air for from two and one-half to sixty-eight hours, the anterior horn cells showed a gradual restitution to their normal appearance. In some of the animals there were marked changes in the chromatic bodies, bleaching,

irregularity of outline, and partial subdivision, at a period when the motor power appeared to be completely restored.

From these very interesting data, the authors conclude that the chromatic bodies of Nissl have no vital importance in the nerve cell, and that their relation to the functions of the cell appears doubtful, since they could not say that the alterations observed were always beyond doubt to be regarded as the substratum of the disturbances of function observed in the animals. Yet they consider their experiments to have shown that malonitril and the artificial elevation of temperature induce a disturbance of function, and, if more active, a simultaneous disturbance in the nutrition of the cell. The functional disturbance may rapidly pass off, but the disturbance of nutrition is very slowly recovered from. Both processes begin together, but later proceed more or less independently of one another.

Having observed in August, 1896, throughout the central nervous system of a case of insolation, lesions identical in many respects with those described by Goldscheider and Flatau in the spinal stichochromes of heated rabbits, the writer was lead to repeat those experiments for the purpose of comparing the lesions with those found in sunstroke, and with the further object of carefully comparing the alterations in the chromatic bodies with the grade of functional disturbances observed in the animals.

The importance of the subject may warrant a report of some of these experiments.

Experiment I.—A medium-sized healthy female rabbit, rectal temperature 38.3° C., was placed at 11.45 A. M., in a dry air oven, in which the temperature ranged between 46° and 48° C. It began to breath rapidly at once. After

one hour it lay panting on its side and seemed very weak, although kicking rather actively when prodded. Temperature 41.5°. After one and one-half hours the animal seemed greatly exhausted, being hardly able to stand. The reflexes were markedly hyperæsthetic and breathing was very rapid. At the expiration of two hours the animal was found dead and rigid. Rectal temperature 44° C.

The examination of the viscera revealed much venous congestion of cerebro-spinal meninges, and lungs. The other viscera were notably pale. The blood was very dark and entirely fluid, failing to clot also after shedding.

The central nervous system was examined, after hardening 24 hours in Lang's fluid, by Nissl's method. In the *medulla* all the chromatic bodies of the nerve cells had disappeared, although some cells showed a faintly visible network or a few dark granules in the cytoplasm. Large, clear vacuoles were seen in some cells. The cell bodies looked waxy, staining light blue, their outlines were usually regular. The nuclei were, almost without exception, diffusely stained dark blue. About the nucleoli were often two to five dark granules, while the nuclear membrane was irregularly invisible. In the *cord*, the chromatic bodies of the stichochromes had almost entirely disappeared, the cell bodies looking waxy, swollen, and staining diffusely light blue, the periphery being very pale. In many cells traces of the chromatic bodies could be detected, (1) in the form of very pale ragged masses of the same general shape as in the normal condition. (2) In the form of fine granules scattered through the cytoplasm, sometimes in the form of a network; and (3) as a diffuse discolorization of the entire cell. The dendrites showed an irregular network composed of granules, or occasionally a ragged spindle. The nuclei were very darkly stained, their position was usually central, and they resembled the nuclei of the medullary cells.

Experiment II. Similar in most respects to the first, except that after two and one-half hours, the animal, with

a rectal temperature of 45° C., was removed from the oven and placed in a draught of fresh air, with the expectation that it would recover. Although the symptoms had been rather less marked than in the first case, one hour later the rabbit was found dead and rigid. Post-mortem appearances and condition of ganglion cells, the same as in former case.

Experiment III. Was undertaken to ascertain more accurately the symptoms occurring before death.

After one hour the rabbit's temperature registered 43°. It lay on its side and was unable to stand for more than a few seconds, falling with very marked tremor. The respirations were 320 per minute and irregular. The reflexes were exaggerated. Placed in a draught for five minutes, it seemed greatly recovered, and sat in a normal position, the respiration falling to 200. After three and one-half hours, the temperature of the oven being 45°, the animal's temperature registered 44.6°, and it was again placed in a draught. At 3 hours, 45 minutes, temperature 43.6°; at 4 hours, 41.6°; at 4½ hours, 39°. The fresh air very rapidly improved the animal's appearance, the respiration became nearly normal, and motor power seemed also normal. The reflexes were still exaggerated. It was again placed in the oven and its temperature raised in one hour to 45°. All the symptoms then returned, spasms of the limbs could readily be elicited, there was one short period of general clonic convulsions, later two general tonic spasms, ending in death, six hours from the beginning, with rectal temperature 45°.

The post-mortem appearances of the viscera and the condition of the ganglion cells throughout the central nervous system did not differ materially from those described in experiment No. 1. These experiments were repeated in a slightly altered form on four other rabbits, without eliciting any new facts in regard to the relation between the symptoms exhibited by the animals and the condition of the ganglion cells of the central nervous system. It may be noted in passing that the amphophilic

network demonstrated in the cells of the liver and kidney of normal animals was partly or completely destroyed in a degree quite comparable to the changes observed in the nerve cells.

The experiments, therefore, bear out completely the conclusions of Goldscheider and Flatau, that artificial elevation of temperature very rapidly distorts or destroys the chromatic structure of the ganglion cells of rabbits.

A further set of experiments was conducted upon rabbits to determine how far the nervous function of these animals could be restored by prompt resuscitation after exposure to high temperatures, and in order to ascertain the condition of the ganglion cells in the resuscitated animals.

The following report will serve to illustrate four very similar experiments of this order:

A medium-sized black field rabbit, temperature 38.5° C, was placed in the oven, temperature 45.7° C at 10 A.M. At 11 A.M. the temperature of the oven was 47° C, that of the rabbit 42° C. The usual symptoms were observed, the animal lay panting but kicked vigorously when prodded. At 12 M. the temperature of oven was 48° C, that of the rabbit 43° C. Dyspnœa was now very marked, and the animal was hardly able to sit up, and it was now placed in a draught for 15 minutes. At 12.45 P.M. the temperature of the oven being 52° C, and that of the rabbit 45° C, it was noted that the respirations had fallen to 134, and shortly thereafter to 100, when breathing became irregular. The circulation was now very feeble. The reflexes were not exaggerated. The animal lay on its side, and could not hold up its head. It was bathed in water for 10 minutes, as death appeared to be imminent, and improved considerably. At 1.15 P.M. its temperature was 44°C. At 2.15 it was running about the room and was difficult to catch. When carefully watched however, it appeared to be partly

blind, as it repeatedly ran into the wall. The reflexes were now extremely exaggerated, the slightest touch starting a violent general tremor with occasional spasms. Circulation and respiration appeared normal. Temperature at 2.15 P.M. 40° C. At 2.40 P.M., temperature 39° C, the animal was rendered unconscious by a light blow on the head and was then exsanguinated, two hours after the last exposure to heat. The examination of the central nervous system revealed the same changes as noted in the previous experiments. In three other experiments the animals were allowed to recover for three and four hours after the last exposure to heat, but no distinct improvement in the nervous condition of the animals and no restitution of the cellular lesions in the nervous system were noted. Having noted, as did Goldscheider and Flatau, a considerable restoration of function in cells presenting extensive alteration or destruction of chromatic structures, it was thought unnecessary to continue these experiments further.

The writer's observations accord with those of Goldscheider and Flatau *with the exception that in the above experiments the cellular lesions were accompanied by a persistent loss of functional capacity as indicated especially by the persistent hyperæsthesia of the reflexes.*

It is, therefore, impossible to fully agree with the claim of the above investigators, that the functions of these extensively altered cells are entirely normal. Moreover, it might well be urged that it is impossible to detect in rabbits many finer disturbances of nervous function such as may be fully recognizable in man, and may, by analogy, be supposed to exist in animals thus treated.

It is well known that patients recovering from sunstroke, a condition in which the writer finds cellular lesions very similar to those in heated rabbits, are very liable to suffer from a variety of functional nervous disorders, including tachycardia, paralysis, and sudden death, and this fact must

stand as evidence that ganglion cells once affected in this way, are not immediately restored to full functional activity. It must be accepted, however, that a considerable grade of functional capacity may remain in cells showing extensive lesions of the chromatic substance.

Further than this the present state of our knowledge does not permit any deductions to be drawn concerning the relation between disordered function and altered structure of the nerve cell. It remains for future investigations to determine, either from peculiar characters of the chromatolysis, or, as seems more likely, from changes in the nucleus and achromatic portion of the cell what degree of functional capacity may remain in cells showing various grades of chromatolysis.

Section VII.

Effects of Hyperpyrexia in the Human Subject.

The effects of artificial elevation of temperature upon the ganglion cells in rabbits naturally raises the suspicion that many of the cellular changes now attributed to various intoxications and infections are referable solely to the pyrexia attending these conditions and do not accurately measure the action of the circulating toxic agent.

Moxter[213] studied the effects of elevation of temperature in rabbits caused by puncture of the medulla after the method of Aronsohn and Sachs. (Ffluger's Archiv., 37, 1885).

In one rabbit whose temperature rose to 41.5°, 23 hours after a second operation, many of the cells of the anterior horn of the cervical cord showed advanced chromatolytic lesions. In four other rabbits killed after repeated operations on successive days, and in which the temperature

varied between 38° and 41° no changes were found in the cells of the cord. The author concludes from this rather meagre evidence that simple elevation of temperature is sufficient to induce chromatolytic lesions in the nerve cells.

Goldscheider and Flatau[214] reach the same conclusions from observing in cases of tetanus and scarlatina, cellular lesions similar to those seen in rabbits heated in the oven.

Throughout the present series of cases the writer has observed a uniform fading of the chromatic substance in addition to other lesions in many cases attended with high fever.

Among such cases may be mentioned—the case of tetanus; Case VII of subacute leptomeningits; Case II of pneumonia; the case of general burns; and the first two cases of sunstroke.

The following case also is believed to be of special interest in this connection. (It will be fully reported later by Doctor Robert Abbe, to whom the writer is indebted for the reference to the nervous system).

Sudden Death after Osteotomy.

Female, five years old. Osteotomy of both tibiæ was performed for bow legs at 3 P. M. July 8. The anæsthesia, by ether, and the operation, lasting thirty minutes, were uneventful and the child was put to bed in apparently good condition. At 6 P. M. the temperature was found to be 103°. At 7 P. M. 105°; at 12 P. M. 106°; at 3 A. M. 109°; at 5.30 A. M. the child died, ante-mortem temperature not taken. During the last nine hours the pulse became very rapid and the respiration rose to 40 per minute, but there was no cyanosis. There were no convulsions or paralysis, no subjective complaints, and no other noteworthy symptoms. The temperature at death was probably 110°.

Autopsy ten hours after death.

The thymus was considerably enlarged, measuring 4 x 5 x 1 cm. There were general evidences of old rachitis. The lymphatic system appeared normal. The lungs were intensely congested and slightly œdematous. The

other viscera were moderately congested. No other lesions were discovered.

Microscopical examination. Formalin 10 per cent.

The question of embolic processes in the lungs and other viscera has not yet been determined, and in any case can prove only of secondary import in the purpose for which this report is now made.

In the *lumbar cord* nearly all cells are extremely faint, the chromatic bodies having faded uniformly without apparent subdivision. They sometimes appear swollen. The nuclei are coarsely granular, and the nucleoli swollen and composed of coarse refractive granules. Some cells are composed exclusively of coarse, faintly bluish stained granules. In a few cells, the perinuclear chromatic bodies persist, but are swollen and considerably faded. The cyto-reticulum is invisible.

In the *cervical cord* the changes are similar but slightly less marked.

In the *spinal ganglia* extreme alterations of the same general type were noted, but the chromatolysis was more marked in the perinuclear areas of the cells; while along the peripheries there was a considerable remnant of chromatic substance but no distinct bodies.

Throughout the *medulla* nearly all the cells are extensively bleached. Many are entirely lacking in chromatic substance. In some the chromatic bodies are still preserved but they are extremely pale, so that their outlines are barely distinguishable. The nucleoli are swollen and very pale. Purkinje's cells are least affected. Most of them show a few distinct chromatic bodies limited to the base or periphery of the cell. The other bodies are either invisible or extremely thin and pale.

In the *motor cortex* there is uniform and extreme reduction in chromatic substance in all the cells.

The above case must be regarded as a specially favorable opportunity of ascertaining in the human subject the effects of high temperature uncomplicated by other toxic influences. The extreme loss of chromatic substance in all regions of the central nervous system can be attributed, it would seem, solely to the pyrexia. Ether does not produce such changes in animals, nor such symptoms in the human subject, and embolic processes could hardly have reached such general distribution as were shown by the lesions in the nerve cells.

The chromatolytic process was here somewhat different from that observed in sunstroke, and in heated rabbits, for the chromatic bodies in both the latter conditions suffered much granular subdivision before disappearing, while in this instance, they appeared to fade usually without granular subdivision.

It is important to note that the nuclei of all the cells in the tissues examined stained with diminished intensity by methylene blue.

From the evidence thus reviewed it seems probable that in cases attended with extreme pyrexia, *i. e.*, above 107° F., extensive bleaching of the great majority of ganglion cells in the central nervous system may indicate only the effects of the febrile process and not those of an associated toxæmia.

On the other hand, the present series offers several instances which prove beyond a doubt that extreme pyrexia lasting many hours may fail to induce such general chromatolytic changes in the ganglion cells. Among these may be mentioned Case IV of pneumonia, and Case III of sunstroke, in which there was high and continuous pyrexia, but extreme examples of chromatolysis occurred in isolated foci only and many cells remained intact.

On the other hand, also, the cases of the present series in which prolonged high temperature of 105° to 106°, failed to induce extreme grades of chromatolysis of general distribution are rather numerous and one is forced to conclude that the ordinary temperature of infectious diseases plays only a limited and secondary part in the chromatolytic changes observed in these conditions.

It is hardly necessary to add that an observation of ante-mortem temperature is an essential in the study of clinical material by Nissl's method.

Section VIII.

General Character of the Lesions in Nerve Cells.

The confusion which has resulted from the use of a variety of terms to designate the same change in the chromatic bodies of the nerve cells, renders it very desirable that a uniform nomenclature should be employed in the description of these lesions. Unfortunately for this end, the different stages of the process of chromatolysis and the effects of different reagents give extremely varied pictures of these changes, although as the writer believes, the process is always essentially one and the same, consisting in a diminution of volume by one means or another of the mass of chromatic substance.

The chromatolytic process is frequently, if not always, initiated by a *preliminary swelling of the chromatic body.* The exact nature of this change is not known, nor has its presence in suitable conditions invariably been noted. Examples of this stage are best demonstrated in the early periods of infection with tetanus, and in artificially heated animals.

Either with or without the preliminary stage, the chromatic substance begins to disappear from the mass. If the change proceeds slowly the chromatic body diminishes uniformly in size, and in the last stages appears as a slender and pale spindle or granule. Such appearances are common in slowly fatal cases of obstruction to cerebral circulation, and the change may be designated *as uniform diminution in size of the chromatic body.* When the lesion advances more rapidly several points in the chromatic body may appear bleached, the mass may be partly subdivided or reticulated, and the process may be designated *as uniform subdivision of the chromatic body.* Many such cells may be seen in the chronic toxæmias.

In many severe and acute lesions the process seems to affect all portions of the chromatic body, reducing it to a series of granules, which at first indistinctly outline the original mass, later are found diffusely scattered throughout the cytoplasm and giving the cell a peculiar dusty aspect. This appearance may be designated as *the granular subdivision of the chromatic body*. The distinctness of the granular appearance, at least in the early stages, will depend much upon the fixing agent employed.

All stages of such alteration may be followed in most cases of acute poisoning.

The final stage of the chromatolytic process may leave the cell entirely lacking in chromatic substance, and showing on close inspection only the original cyto-reticulum which is usually demonstrable by methylene blue. This stage is usually spoken of as *complete simple chromatolysis*.

Whatever variation there may be in the intermediate stages, the end results of simple chromatolysis are usually identical. The writer has been unable to find upon close scrutiny any essential difference in the structure of the badly altered cells in sunstroke, alcoholism, thrombosis of the basilar artery, cerebral hemorrhage, the acute and chronic toxæmias, and most of the cells in tetanus.

In most of these cases the complete bleaching of the cell has been reached without demonstrable changes in the cytoplasm or nucleus.

It is usual for the chromatolytic process to affect exclusively the perinuclear zone (*central chromatolysis*), or the peripheral areas (*peripheral chromatolysis*), or, at times, one or more segments of the body (*circumscribed chromatolysis*). Often all the chromatic bodies are uniformly subdivided, occasionally only the dendritic masses.

The well known appearance of the cell affected by

central chromatolysis and eccentricity of the nucleus has been aptly termed by Van Gieson the "axonal degeneration."

During the process of chromatolysis, however, other changes are often described, affecting the achromatic substance and the nucleus. Thus a *diffuse staining of the achromatic substance* is often reported in the examination of the cells, pointing either to a diffusion of the chromatic substance into the achromatic, or to a chemical alteration of the cytoplasm. Nearly every pathological specimen contains cells of this appearance, yet it is far from certain that the achromatic substance ever really exhibits an increased affinity for methylene blue. Without insisting that such is invariably the case, the writer is convinced that the vast majority of these appearances are artificial, resulting from incomplete decolorization, an unusually thick section of cell body which may occupy the entire depth of the cut section, and from the diffused blue refraction of finely subdivided chromatic bodies. See Plate IV, Fig. 2. Such cells are very striking in the cords of heated rabbits, but the diffuse bluish stain disappears in very thin sections.

Likewise nuclear chromatophilia in thin sections disappears or resolves itself into the presence of numerous fine granules in the intranuclear network.

The significance of vacuolation has already been discussed.

It is very probable that vacuoles may form in moderate numbers and of small size from vital patholgical processes, in which case their presence indicates a true degenerative change in the cell body.

Rupture of dendrites has often been referred to as a vital pathological process, but it is far from clear that the

condition results from any other influence than traumatism, applied either in extracting the brain and cord from the body, or resulting from the shrinkage of tissues during the hardening process.

The finer changes in the achromatic substance it is impossible in the present state of our knowledge to describe accurately. In the majority of cells that have lost their chromatic bodies a delicate cyto-reticulum remains visible. In many of the severe toxæmias and especially in the acute infections of the nervous system, as tetanus, hydrophobia, myelitis, etc., this cyto-reticulum may be found to be irregular, coarsely granular, distorted by vacuoles, or may become invisible. In some instances the coarse granules may show slightly altered staining reactions and refrangibility, and in some of the writer's cases, these granules seemed to approach the character of the ordinary yellowish pigment deposit.

The *formation of clefts and fissures* is a distinct feature of the lesions of the achromatic substance as seen in various conditions. These changes, while of great interest, as bearing on the structure of the ganglion cell, have not yet received any explanation.

The entire cell body may be found to be slightly *swollen*, especially in the early stages of chromatolysis. In simple chromatolysis no changes in the size or contour of the cell body is ordinarily found. In most human subjects dying from general diseases, some cells exhibit *irregularity in outline* which indicates a true degenerative process, affecting all elements. The possible effects of reagents must here, of course, be constantly recognized.

In lesions of longer standing, the cell body may be markedly *shrunken*, its *outlines rounded*, the *dendrites may disappear*, the chromatic substance is entirely wanting,

and the *cytoplasm* may appear uniformly and coarsely *granular*.

A considerable variety of nuclear changes has been described.

The nucleus is often *shrunken*, but it is difficult to see what vital process can induce such a change, and its significance is as yet uncertain.

A peculiar appearance sometimes encountered, and depicted in Plate VI, Fig. 5, is the gathering of granules and rods of chromatic substance about one side of a shrunken nucleus. This change also is without known significance. The *nuclear membrane may be invisible* in specimens stained by methylene blue. In some of these cells a counterstain by erythrosin may demonstrate a faint persisting membrane, or, in other instances, this structure seems to have entirely disappeared.

The intra-nuclear network is often replaced by a series of pale granules, very irregular in size and position. The character and location of these granules is fully demonstrated by erythrosin.

Nuclear chromatophilia the writer must refer to the presence of many of these fine granules or to an underlying stratum of the cell body containing finely subdivided chromatic bodies, having rarely encountered a diffuse staining of this body apart from post-mortem processes.

The *nucleolus* is sometimes distinctly *swollen*, and thin sections of such nucleoli, usually discloses a reticulated structure. Some of the meshes of this reticulum may project beyond the border of the nucleolus, giving the appearance of vacuolation. In such cases the changes in the central acidophile mass of the nucleolus may be followed in sections stained by Ehrlich's tricolor mixture.

The nucleus may contain several large or small deeply

staining masses grouped about the nucleolus, and suggesting a subdivision of this body. In these granules, often called *secondary nucleoli*, the writer has been unable to demonstrate any portion of the central acidophile mass of the nucleolus, and it appears that their origin is not certainly understood.

While the above changes in the ganglion cells as demonstrated by Nissl's method are those most frequently encountered, any attempt to exhaust all the possible peculiarities of the degenerating nerve cell must necessarily be fruitless. The minute lesions appear to differ in each case and the range of minor peculiarities is practically limitless. Especially in the advanced stages of acute and chronic degeneration the aspect of the cells may be so heterogeneous that classification of lesions is impossible.

Likewise the attempt to separate the lesions of simple chromatolysis from those of true degeneration, requires, in the present state of microscopical technics, too much conjecture for the conservative investigator, especially as the physiological and pathological processes are usually blended. The early stages of the true degenerative process have not yet been satisfactorily demonstrated, and it is only when we meet with vacuolation of the cell body, with clefts, raggedness of outline, destruction of cyto-reticulum, loss of dendrites, and distinct atrophy, and when marked nuclear changes are present, that it is safe to conclude that a generally destructive process has been at work. *When acute degeneration, in a strict sense, affects the ganglion cell, its changes are usually evidenced by various forms of chromatolysis, but the true degenerative process may not and, as the writer believes, frequently does not begin until after chromatolysis is complete.*

DESCRIPTION OF PLATES.

Plate I.

Figure 1.—"Polar dendrite" of lumbar stichochrome. Specimen teased in fresh condition, fixed by heat, stained by erythrosin and methylene blue.

The chromatic bodies appear as integral parts of the reticulum, the blue fading insensibly into the red threads. The reticulated portion of the cell is sharply marked off from an envelop of granular acidophile substance which is continuous with the axis cylinder process.

Figure 2.—Normal human Purkinje cell. Specimen teased in fresh condition, fixed by heat, stained by methylene blue. The chromatic bodies are continuous with a network staining distinctly with methylene blue.

Figure 3.—Normal human archystichochrome, from motor cortex. Sat. aqueous bichloride. Methylene blue.

Figure 4.—Normal human spinal ganglion cell. Van Gehuchten's fluid. Methylene blue.

The large chromatic bodies are concentrically arranged. The achromatic substance at the pole is finely granular, and the granules are placed in indistinct radiating rows. These granules do not stain distinctly as does the reticulum of the cell body.

Plate II.—Cadaveric Changes.

Figure 1.—Medullary stichochrome of infant. Eight hours after death. Lang's fluid. Methylene blue. Very rapid and extreme vacuolation. Loss of cyto-reticulum. Coarsely granular appearance of chromatic bodies. Beginning nuclear chromatophilia.

Figure 2.—Cortical arkyochrome of rabbit, after 36 hours exposure to air. Lang's fluid. Methylene blue. Vacuolation. Coarsely granular appearance of chromatic reticulum. Complete nuclear chromatophilia. Shrinkage of dendrites.

Figure 3.—Purkinje cell of rabbit, after 48 hours exposure to air. Lang's fluid. Methylene blue. Extreme vacuolation. Growth of

putrefactive bacteria. The chromatic reticulum and bodies are reduced to a series of coarse dark granules. Complete nuclear chromatophilia. Shrinkage and destruction of dendrites.

Plate III.—Cadaveric Changes.

Figure 1.—Human Purkinje cell. Twenty-four hours after death. Lang's fluid. Methylene blue. Slight vacuolation. Coarsely granular appearance of chromatic structures. Beginning nuclear chromatophilia.

Figure 2.—Human cortical arkyochrome. Twenty-four hours after death. Lang's fluid. Methylene blue. Slight vacuolation. Partial destruction of chromatic reticulum. Beginning nuclear chromatophilia.

Figure 3.—Human cortical arkyochrome. Twelve hours after death from fracture of vertebra. Lang's fluid. Methylene blue. The chromatic reticulum is replaced by coarse granules. The nuclear membrane and network are markedly thickened.

Figure 4.—Spinal stichochrome of asphyxiated infant. Ten hours after death. Lang's fluid. Methylene blue. Rapid destruction of chromatic structures, which are reduced to coarse granules, some of which are deposited in the pericellular lymph space.

Plate IV.

Figure 1.—Large archystichochrome of motor cortex in case of sunstroke. Sat. aqueous bichloride. Methylene blue. The chromatic bodies have entirely disappeared, leaving a fine reticulum staining faintly with methylene blue. The nucleus contains several large granules, probably derived from the nucleolus.

Figure 2.—Medullary stichochrome of rabbit, killed by heating. Sat. aqueous bichloride. Methylene blue. (Section 3 μ. Zeiss $\frac{1}{18}$ apochromatic lens; artificial light; achromatic condenser; oil on condenser).

By low magnification, this cell appears uniformly homogeneous and diffusely stained. On higher magnification and special illumination, the cell is found to contain remnants of the chromatic bodies in the form of fine, pale granules. No cyto-reticulum could be discerned.

Figure 3.—Human cortical archystichochrome, in case of tetanus. Alcohol, 97 per cent. Methylene blue. The chromatic masses are almost entirely wanting, the faint chromatic network persisting. The intra-nuclear network is thickened and coarsely granular and the nucleolus presents several small clear areas.

Figure 4.—Human medullary stichochrome, in a case of sunstroke. Section 3 μ. Sat. aqueous bichloride. Methylene blue. The chromatic bodies are destroyed. The cell is largely composed of coarse pale granules, which sometimes form an indefinite chromatic network. The cell borders are rounded and the processes missing.

In sections 15 μ in thickness this cell appeared uniformly homogeneous and chromatophilic, as in the small figure.

Figure 5.—Purkinje cell in case of thrombosis of basilar artery. Lang's fluid. Methylene blue. There is uniform fading and marked diminution in size of the chromatic masses. The cyto-reticulum is very indistinct in the cell body, but a reticulum staining with methylene blue is visible in the dendrites.

Plate V.

Figure 1.—Cortical arkystichochromes compressed by distended capillary in case of acute uræmia (Case I). In both cells there is moderate perinuclear chromatolysis with preservation of reticulum.

Figure 2.—Usual changes in cortical cells in uræmia.

In the arkyochrome the network is distinct but its meshes are not always uniform in size. The nucleus contains many large pale granules replacing the intranuclear network. In the arkystichochrome there is moderate perinuclear chromatolysis and certain nuclear changes.

Plate VI.

Figure 1.—Human Purkinje cell in case of tetanus. Alcohol 97 per cent. Methylene blue. There is marked fading and partial subdivision of chromatic bodies. The reticulum of the cell body is indistinct and irregular but appears much sharper in the dendrites. The nuclear membrane is almost invisible and the intranuclear network is reduced to coarse pale granules. The nucleolus is distorted and presents the appearance of vacuoles.

This cell must be regarded as showing true degenerative changes.

Figure 2.—Medullary stichochrome adjacent to a miliary tubercle in Case I of tuberculous meningitis. Lang's fluid. Methylene blue. There is moderate subdivision of chromatic bodies especially about the nucleus. A chromatic network is visible between the bodies. The nucleus appears normal.

Figure 3.—Deep medullary stichochrome in above case of tuberculous meningitis. The chromatic bodies are entirely wanting. A faint reticulum persists, staining slightly with methylene blue. Some processes appear to have been destroyed. The nucleus is shrunken and eccentric.

Figure 4.—Axonal degeneration. Sunstroke, etc. Sat. aqueous bichloride. Methylene blue. The chromatic bodies have disappeared from the centre of the cell, leaving a chromatic network and a few fine granules. The nucleus is eccentric, but is otherwise slightly altered.

Figure 5.—Medullary stichochrome in case of acute morphine poisoning. Van Gehuchten's fluid. Methylene blue. The chromatic bodies in several parts of the cell are partly or completely destroyed leaving a faint chromatic reticulum. Some of the remaining bodies appear to have been fused together. The nucleus is shrunken and eccentric. The deeply staining rods heaped about the edge of the nucleus were abundantly present in this cell and are possibly referable to the shrinkage of the nucleus.

Figure 6.—Purkinje cell in case of eclampsia. Lang's fluid. Methylene blue. The chromatic bodies are much faded and partly subdivided. A chromatic reticulum is visible. The nucleolus is enormously swollen, the nucleus is small and markedly chromatophilic.

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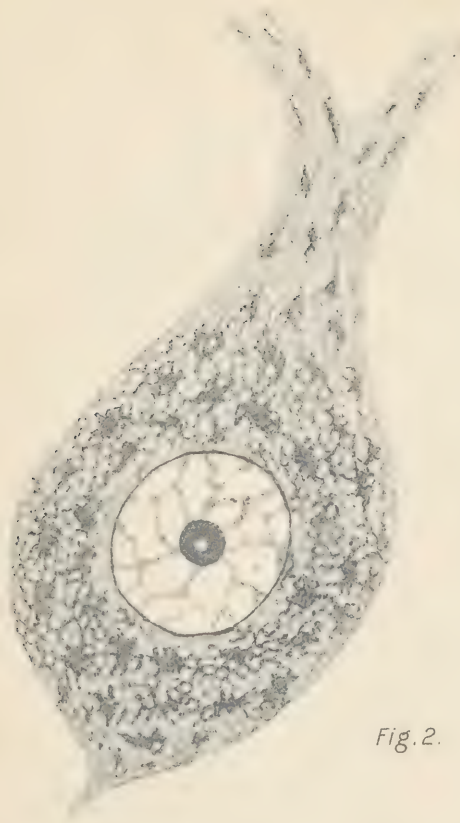

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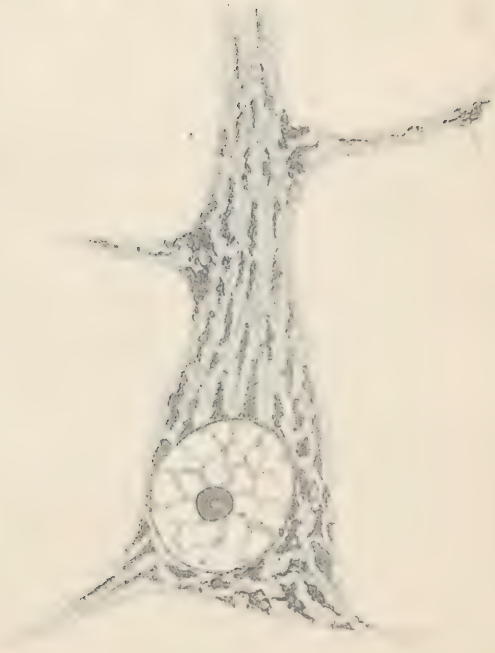

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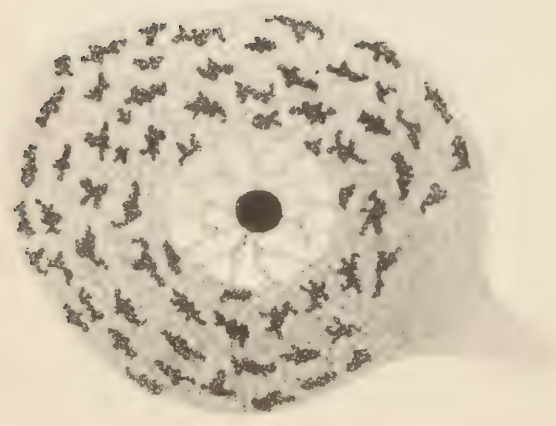

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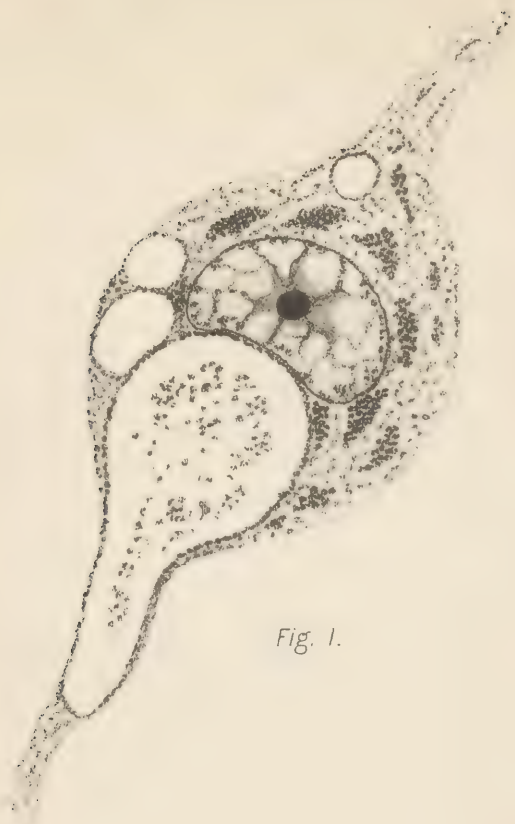

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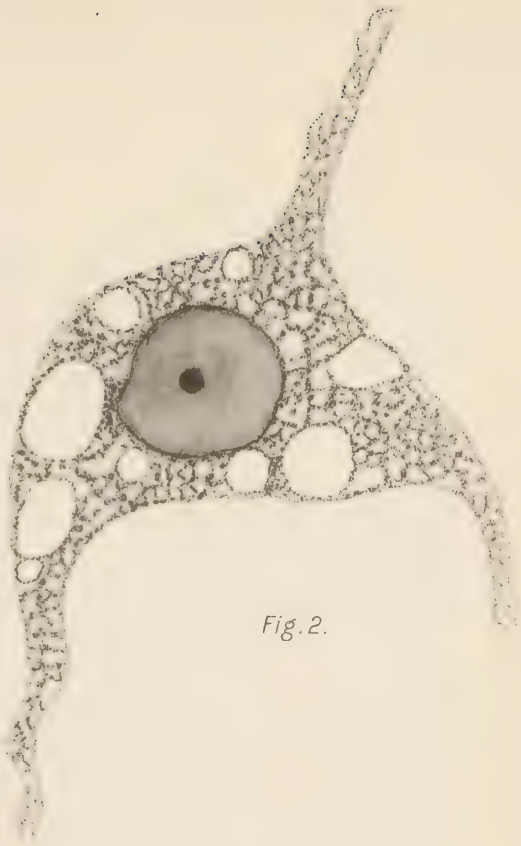

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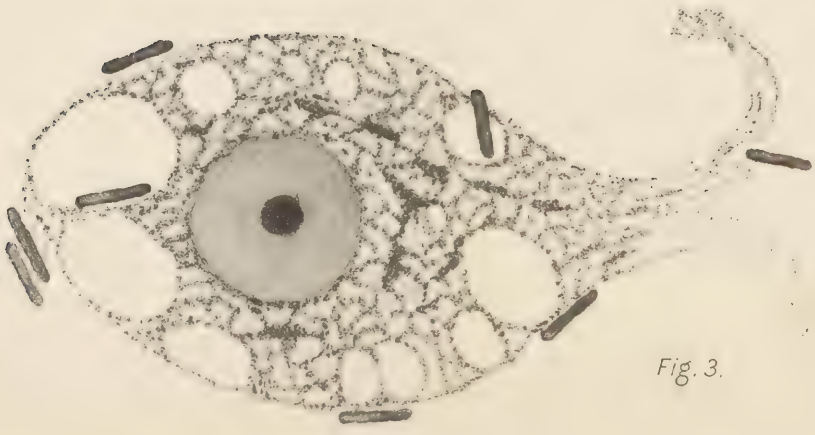

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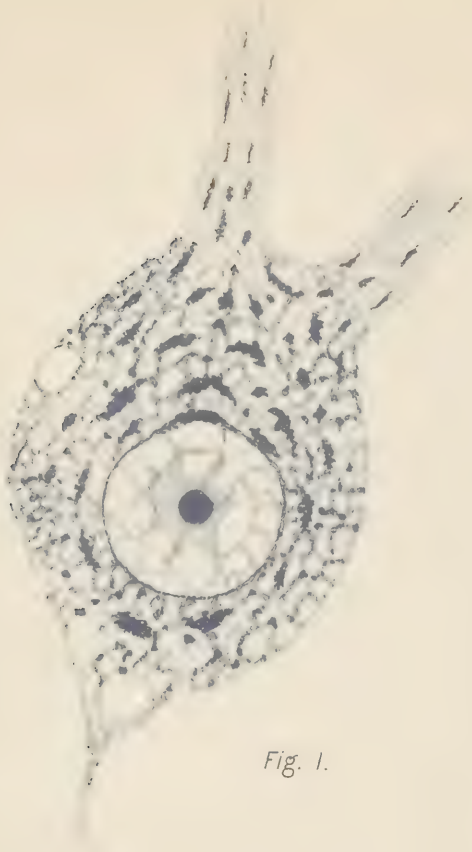

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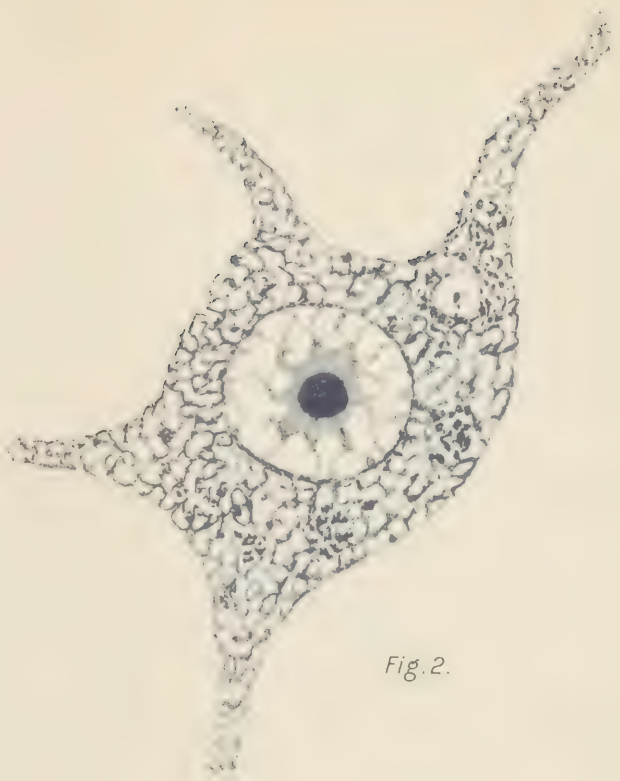

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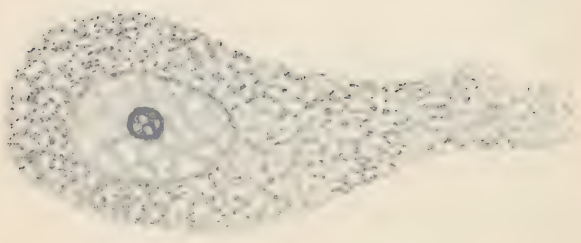

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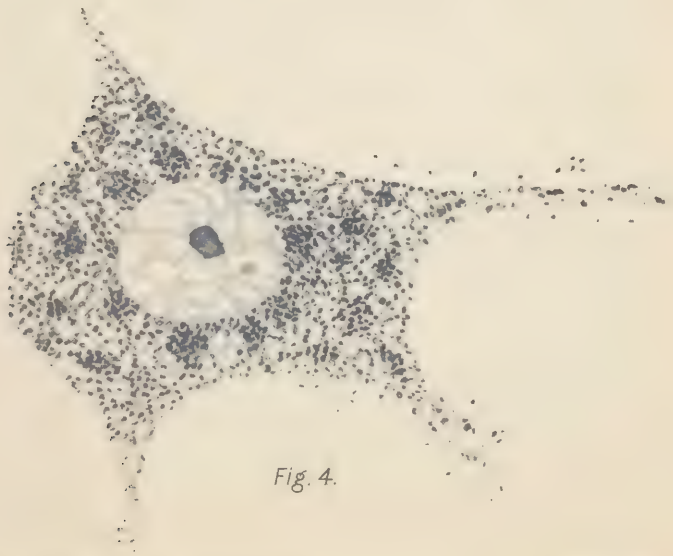

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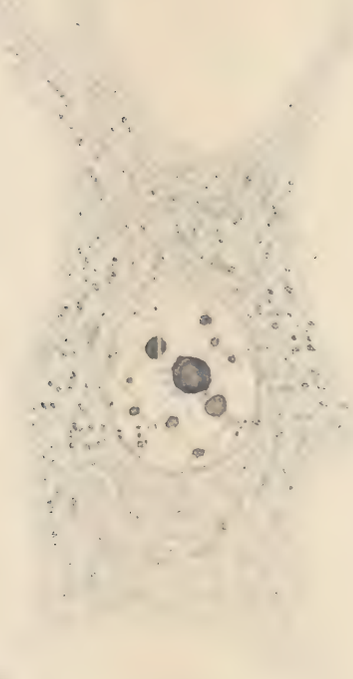

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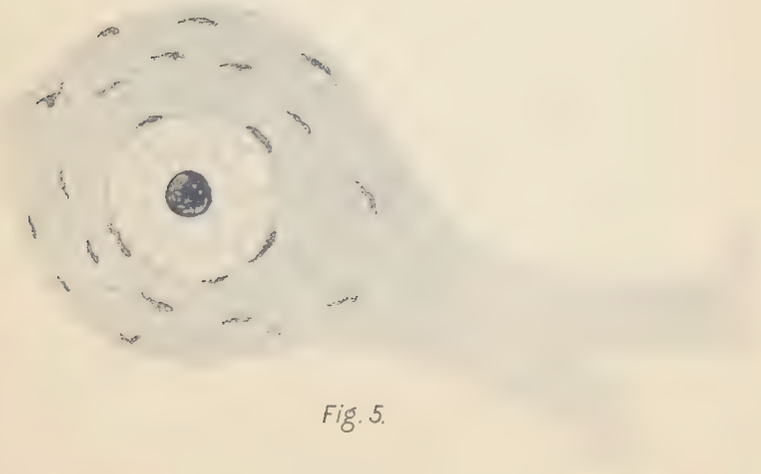

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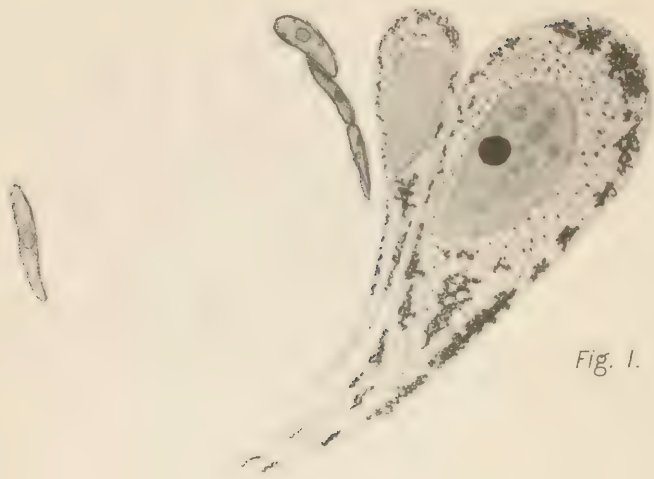

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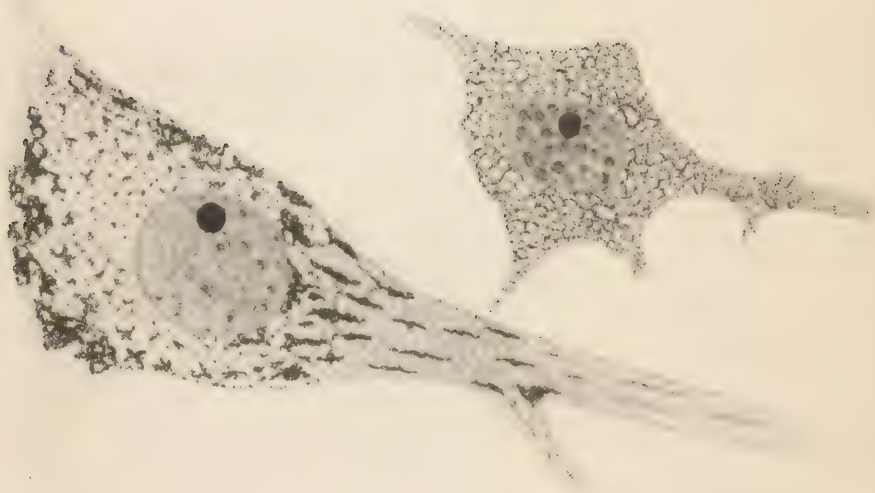

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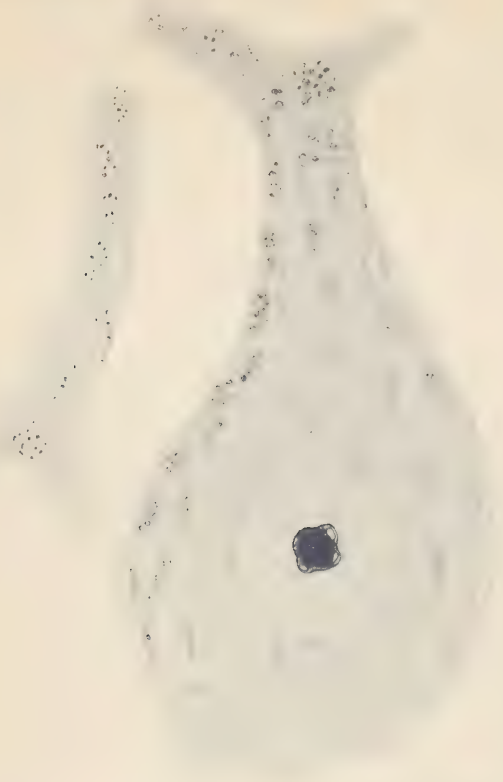

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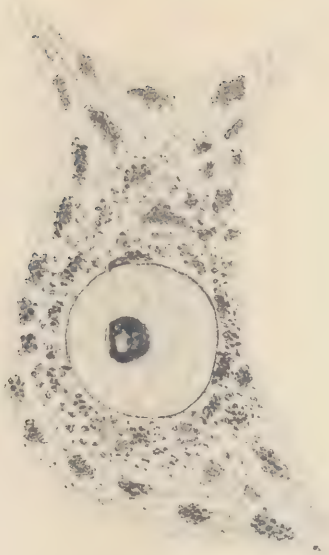

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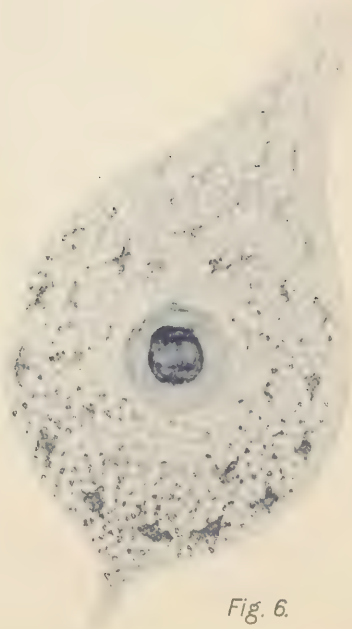

Fig. 6.

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BY SUBJECTS.

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